No. 17-1480

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC.,

Plaintiffs-Appellees

v.

SANOFI; AVENTISUB LLC; REGENERON PHARMACEUTICALS, INC.; AND SANOFI-AVENTIS U.S. LLC,

Defendants-Appellants

On Appeal from the United States District Court for the District of Delaware, No. 14-CV-1317-SLR

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March 24, 2017

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CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellees Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc. certifies the following:

1. The full names of the parties represented by me are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

2. The names of the real parties in interest are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

3. Amgen Inc. owns 10 percent or more of the stock of Amgen Manufacturing, Limited and Amgen USA, Inc. No publicly held company owns 10 percent or more of Amgen Inc.

4. The names of all firms and the partners or associates that appeared for the parties now represented by me in the trial court or are expected to appear in this Court are:

AMGEN INC.: Stuart L. Watt; Wendy A. Whiteford; Erica S. Olson; Dennis J. Smith; Emily C. Johnson; Steven Tang

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March 24, 2017

/s/ Daryl L. Joseffer
Daryl L. Joseffer

TABLE OF CONTENTS

CERTIFICATE OF INTEREST i

TABLE OF AUTHORITIES v

STATEMENT OF RELATED CASES xi

COUNTERSTATEMENT OF THE ISSUES 1

INTRODUCTION 2

COUNTERSTATEMENT OF FACTS 7

I. Technological Background 7

A. Antibody Science 7

B. Amgen's Invention 9

C. FDA Approval of Repatha 17

II. Amgen's Patents 18

III. Defendants' Infringement 20

IV. Procedural History 22

A. This Lawsuit 22

B. Pre-trial Rulings 22

1. Exclusion of post-priority-date evidence 22

2. Obviousness rulings 24

C. The Jury Trial 25

D. The Post-Trial Orders 26

1. Denial of JMOL 26

2. Denial of a new trial 28

3. Granting of a permanent injunction 28

SUMMARY OF ARGUMENT 31

ARGUMENT 33

I. Defendants Are Not Entitled To A New Trial. 33

A. The Court Did Not Abuse Its Discretion In Excluding Post-Priority-Date Evidence. 33

1. The evidence was irrelevant. 34

2. The evidence would have confused the jury. 37

B. The Court Properly Instructed The Jury On The "Newly-Characterized Antigen" Test. 41

1. The instruction correctly stated the law. 41

2. The "newly-characterized antigen" test is sound. 44

3. The wording of the instruction was not in error. 46

4. Any error was harmless. 48

C. The Court Properly Granted JMOL Of Non-Obviousness. 48

II. Defendants Are Not Entitled To JMOL On Written Description Or Enablement. 55

A. Defendants Waived JMOL. 55

B. Extensive Evidence Supports The Written-Description Verdict. 56

1. Representative species. 57

2. Common structural features 61

3. The "newly-characterized antigen" test 65

C. Extensive Evidence Supports The Enablement Verdict. 67

III. The District Court Did Not Abuse Its Discretion In Granting A Permanent Injunction. 69

A. Ongoing Infringement Is Causing Irreparable Harm To Amgen Not Adequately Compensable By Damages. 71

B. The Balance Of Harms Does Not Favor Infringers Who Knowingly Assume The Risk Of An Injunction. 74

C. The Public Interest Is Not Disserved By An Injunction. 75

1. Defendants and *amici* distort the court's findings. 75

2. The injunction does not leave patients without safe, effective treatment. 77

3. The court had discretion to balance the factors. 81

CONCLUSION 82

CERTIFICATE OF COMPLIANCE

CERTIFICATE OF SERVICE

TABLE OF AUTHORITIES

Cases

Abbott GMBH & Co., KG v. Centocor Ortho Biotech Inc.,
870 F. Supp. 2d 206 (D. Mass. 2012) 35

Abbott Labs. v. Mead Johnson & Co.,
971 F.2d 6 (7th Cir. 1992) 81

AbbVie Deutschland GmbH v. Janssen Biotech, Inc.,
759 F.3d 1285 (Fed. Cir. 2014)....................................... 4, 34, 35, 60

Abrams v. Lightolier Inc.,
50 F.3d 1204 (3d Cir. 1995)... 41

Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.,
344 F.3d 1186 (Fed. Cir. 2003)... 56

Alexander Milburn v. Davis-Bournonville,
46 S. Ct. 324 (1926) 52

Alexander v. Riga,
208 F.3d 419 (3d Cir. 2000)... 47

Amgen v. Hoechst Marion Roussel, Inc.
314 F.3d 1313 (Fed. Cir. 2003)... 35

Amgen, Inc. v. F. Hoffman-La Roche Ltd.,
581 F. Supp. 2d 160 (D. Mass. 2008),
aff'd in part, *rev'd in part on other grounds*,
580 F.3d 1340 (Fed. Cir. 2009)... 70

Apple Inc. v. Samsung Elecs. Co.,
735 F.3d 1352 (Fed. Cir. 2013)... 81

Apple v. Samsung Elecs.,
809 F.3d 633 (Fed. Cir. 2015)... 70

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010)...passim

Ass'n for Molecular Pathology v. Myriad Genetics,
133 S.Ct. 2107 (2013) 47

Bettcher Indus., Inc. v. Bunzl USA, Inc.,
661 F.3d 629 (Fed. Cir. 2011)... 48

Boyle v. United States,
556 U.S. 938 (2009) 47

Capon v. Eshhar,
418 F.3d 1349 (Fed. Cir. 2005)... 37

Centocor Ortho Biotech, Inc. v. Abbott Labs.,
636 F.3d 1341 (Fed. Cir. 2011)..passim

Chiron Corp. v. Genentech, Inc.,
363 F.3d 1247 (Fed. Cir. 2004)... 35

Cordance Corp. v. Amazon.com, Inc.,
658 F.3d 1330 (Fed. Cir. 2011)... 57

Cordis Corp. v. Medtronic AVE, Inc.,
339 F.3d 1352 (Fed. Cir. 2003)... 37

Cordis v. Boston Sci.,
99 F. App'x 928 (Fed. Cir. 2004) 70

Douglas Dynamics, LLC v. Buyers Prods.,
717 F.3d 1336 (Fed. Cir. 2013)... 71, 72

Duro-Last, Inc. v. Custom Seal, Inc.,
321 F.3d 1098 (Fed. Cir. 2003)... 55

Dynamic Drinkware LLC v. Nat'l Graphics, Inc.,
800 F.3d 1375 (Fed. Cir. 2015)... 49, 50, 53

eBay v. MercExchange, L.L.C.,
547 U.S. 388 (2006) 29, 81

Egan v. Del. River Port Auth.,
— F.3d —, 2017 WL 1055568 (3d Cir. 2017).................................. 38

Enzo Biochem, Inc. v. Gen-Probe Inc.,
323 F.3d 956 (Fed. Cir. 2002).. 42, 44, 46, 56

Estelle v. McGuire,
502 U.S. 62 (1991) 47

Ex Parte Supuran,
2011 WL 1661465 (BPAI Apr. 28, 2011) 66

Ex Parte Xia,
2009 WL 220277 (BPAI Jan. 28, 2009) 66

Falko-Gunter Falkner v. Inglis,
448 F.3d 1357 (Fed. Cir. 2006)... 63

FMC Corp. v. United States,
3 F.3d 424 (Fed. Cir. 1993)... 81

Hecht Co. v. Bowles,
321 U.S. 321 (1944) 81

i4i Ltd. P'ship v. Microsoft Corp.,
598 F.3d 831 (Fed. Cir. 2010)... 55, 72, 74

In re Giacomini,
612 F.3d 1380 (Fed. Cir. 2010)... 50, 54

In re Hogan,
559 F.2d 595 (C.C.P.A. 1977) 34

In re Koller,
613 F.2d 819 (C.C.P.A. 1980) 34

In re Wallach,
378 F.3d 1330 (Fed. Cir. 2004)... 36

In re Wands,
858 F.2d 731 (Fed. Cir. 1988)... 67

In re Wertheim,
646 F.2d 527 (C.C.P.A. 1981) 50

Janssen Prods., L.P. v. Lupin Ltd.,
109 F. Supp. 3d 650 (D.N.J. 2014) 70

Johns Hopkins Univ. v. Cellpro, Inc.,
152 F.3d 1342 (Fed. Cir. 1998) 67

Merial Ltd. v. Cipla Ltd.,
681 F.3d 1283 (Fed. Cir. 2012) 71

Mytee Prods. Inc. v. Harris Research Inc.,
439 F. App'x 882 (Fed. Cir. 2011) 73

New Railhead Mfg. v. Vermeer Mfg.,
298 F.3d 1290 (Fed. Cir. 2002) 50, 54

Noelle v. Lederman,
355 F.3d 1343 (Fed. Cir. 2004) 42, 43, 44, 60

Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.,
315 F.3d 1335 (Fed. Cir. 2003) 35

Polymer Techs. v. Bridwell,
103 F.3d 970 (Fed. Cir. 1996) 71

Presidio Components, Inc. v. Am. Tech. Ceramics Corp.,
702 F.3d 1351 (Fed. Cir. 2012) 81

Regents of the Univ. of Cal. v. Eli Lilly & Co.,
119 F.3d 1559 (Fed. Cir. 1997) 37

Robert Bosch, LLC. v. Pylon Mfg.,
659 F.3d 1142 (Fed. Cir. 2011) 69, 74, 76, 82

Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA,
821 F. Supp. 2d 681 (D.N.J. 2011) 70

Sanofi-Synthelabo v. Apotex, Inc.,
470 F.3d 1368 (Fed. Cir. 2006) 69

Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.,
637 F.3d 1269 (Fed. Cir. 2011) 34, 38, 41

Smith & Nephew, Inc. v. Interlace Med., Inc.,
955 F. Supp. 2d 69 (D. Mass. 2013) 82

SRI Int'l v. Matsushita Elec. Corp. of Am.,
775 F.2d 1107 (Fed. Cir. 1985) (en banc) 37

Stormans, Inc. v. Selecky,
586 F.3d 1109 (9th Cir. 2009) 80

Therasense Inc. v. Becton Dickinson & Co.,
593 F.3d 1325 (Fed. Cir. 2010).. 48

U.S. Steel Corp. v. Phillips Petroleum Co.,
865 F.2d 1247 (1989) 35

United States v. Downing,
753 F.2d 1224 (3d Cir. 1985).. 38

United States v. Long,
574 F.2d 761 (3d Cir. 1978).. 38

Univ. of Rochester v. G.D. Searle & Co.,
358 F.3d 916 (Fed. Cir. 2004).. 37, 64

WBIP, LLC v. Kohler Co.,
829 F.3d 1317 (Fed. Cir. 2016)... 76

Winter v. NRDC,
555 U.S. 7 (2008) 82

Statutes

35 U.S.C. § 102.. 24, 49, 52, 53

35 U.S.C. § 102(b) 53

35 U.S.C. §102(e)(1) (2006)... 49

35 U.S.C. § 112...passim

35 U.S.C. § 119 (e) ....passim

35 U.S.C. § 122(b)(2)(a)(iii) (2006) 49

Other Authorities

4 Ann. Patent Digest § 32:159:32 73

Lilly Development Pipeline, (http://bit.ly/2nDxgko) 44

Patent and Trademark Office's Manual of Patent Examining Procedure 5, 43

Ray, K. K., et al., *Reductions in Atherogenic Lipids and Major Cardiovascular Events*, CIRCULATION, 134:1931 (2016) 78

Sabatine, Marc S., et al., *Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease*, N ENGL J MED, DOI: 10.1056/NEJMoa1615664 (March 17, 2017) 78

U.S.P.T.O., *Antibody Decisions and Their Compliance with the Written Description Requirement,* [ARCHIVED] (http://bit.ly/2kLrTLa).... 43

U.S.P.T.O., Powerpoint of 10/7/2015 CBT (http://bit.ly/2nMsWPU) 43

Rules

Fed. R. Civ. P. 51 47

Fed. R. Evid. 403 37

Fed. R. Evid. 702 38

STATEMENT OF RELATED CASES

Amgen is not aware of any related cases.

COUNTERSTATEMENT OF THE ISSUES

I. Whether Defendants have shown an abuse of discretion in the court's exclusion of post-priority-date evidence that was irrelevant, cumulative, and confusing to the jury.

II. Whether the court correctly instructed the jury on the "newly-characterized antigen" test that this Court has adopted for written description of antibody claims.

III. Whether the court properly granted judgment as a matter of law (JMOL) on Defendants' obviousness defense because, under this Court's precedents, the art on which they relied was not prior art.

IV. Whether substantial evidence supports the jury's verdict on written description and enablement.

V. Whether the court abused its discretion in enjoining Defendants' admittedly infringing product from the market.

INTRODUCTION

Significant inventions deserve meaningful patent protection both in claim scope and in enforcement by injunction. Amgen's patent claims are valid over the prior art, commensurate with the scope of the disclosure, and fully described and enabled. Defendants failed to prove otherwise: both the jury and the trial court rejected their positions. And the court, recognizing the irreparable harm to Amgen and the inadequacy of damages as a remedy in a head-to-head competitive market, properly gave force to Amgen's patents by issuing an injunction.

The patents in this case disclose breakthrough inventions providing new therapeutic antibodies that dramatically lower levels of LDL-cholesterol ("LDL-C"). As the trial record established, Amgen scientists were the first to invent and describe antibodies that bind to a specific region of the target protein, PCSK9, and block the interaction of PCSK9 with LDL receptors ("LDLR"). The inventors elucidated the relationship between PCSK9 and LDLR and described in detail the small "sweet spot" where the antibodies must bind on PSCK9 to effectively block LDLR and lower LDL-C.

Amgen's patents provide a wealth of disclosure far greater than any antibody patent previously reviewed by this Court. The patents describe the generation of thousands of antibodies to PCSK9 and the screening methods used to isolate 100 antibodies that blocked the PCSK9-LDLR interaction by greater than 90%. The patents disclose the amino-acid sequences for 24 different antibodies, binning data and blocking data that confirm these antibodies bind at the sweet spot, and crystal structures mapping the sweet spot at atomic-level detail.

Defendants are admitted infringers that took the business risk of developing a competing antibody in the face of Amgen's patent rights. Defendants knew that Amgen was the innovator here. Early on, with Amgen's published patent application in hand, they recognized that there would be a "patent issue" because of where their antibody bound to PCSK9.

Amgen filed first with the FDA for approval of its antibody therapy, Repatha. Defendants' response was to use a priority review voucher, which they purchased for $67.5 million from a third party, to leapfrog Amgen in the FDA review queue. As a result, Defendants were the first to obtain FDA approval and to launch their product, betting that they could prove the patents invalid or that the court would not enjoin them. They were wrong on both counts. Their aggressive decisions are the cause of every harm Defendants now assert they will suffer.

Having litigated and lost at trial, Defendants now ask this Court to retry facts and to redo discretionary decisions made by the district court. But none of their arguments comes close to meeting Defendants' heavy burden on appeal of showing the trial court abused its discretion or made errors of law, or that the jury verdict was not supported by substantial evidence.

The errors in Defendants' positions are easily revealed. Defendants argue that this Court's decision in *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014), "foreclosed" the trial court's discretion to exclude irrelevant, confusing, and cumulative post-priority-date evidence. But *AbbVie* does not say anything about post-priority-date evidence, let alone require its admission at trial.

Defendants argue that the court's "newly-characterized antigen" jury instruction was based on "withdrawn" Patent and Trademark

Office ("PTO") guidelines. But the instruction came directly from this Court's decisions. It is also included in PTO's current Manual of Patent Examining Procedure ("MPEP"), and is the basis for PTO Board decisions on examination of antibody claims.

On their obviousness defense, Defendants failed to show their post-priority-date references—two third-party patent applications—were entitled to claim priority back to earlier provisional filings. Under 35 U.S.C. Section 119(e) and this Court's decisions, a reference application is entitled to a provisional's filing date only if the provisional provided written description and enablement support for the reference application's claimed invention—a showing Defendants did not even try to make.

Defendants waived JMOL on written description and enablement by not moving for it at trial. Now, they fail to apply the correct legal standards for JMOL. Simply citing their own witnesses' testimony—while failing to even address most of Amgen's evidence—and asking this Court to find the facts in their favor does not come close to meeting Defendants' burden for reversing the jury verdict. The evidence showed that given the advanced state of antibody technology, the patents' disclosure more than adequately described and enabled the claimed antibodies.

The court granted the permanent injunction because it balanced the four injunction factors and concluded that the public interest in choice did not override the irreparable harm to Amgen and the lack of an appropriate remedy in damages. Defendants do not show this was an abuse of discretion. Contrary to Defendants' repeated refrain, the court did not find that its injunction would "disserve" the public interest.

While asserting their support for a "robust" patent system, Defendants and their *amici* would narrow antibody claims to cover only the specific antibodies exemplified in the patent and described by amino-acid sequence. But narrow claims would allow competitors, like Defendants and *amici* Eli Lilly and Pfizer, to enter a market already fully served by Amgen's Repatha. Limited patent protection is a big disincentive to the pursuit of real innovation because it would be so easy, and less risky, to develop an additional antibody to a validated target instead of blazing new research trails to find new targets and provide new cures. Similarly, denying an injunction and ordering an unprecedented compulsory license would cripple the industry that relies most heavily on patents to protect the huge investment needed to develop breakthrough therapeutic products.

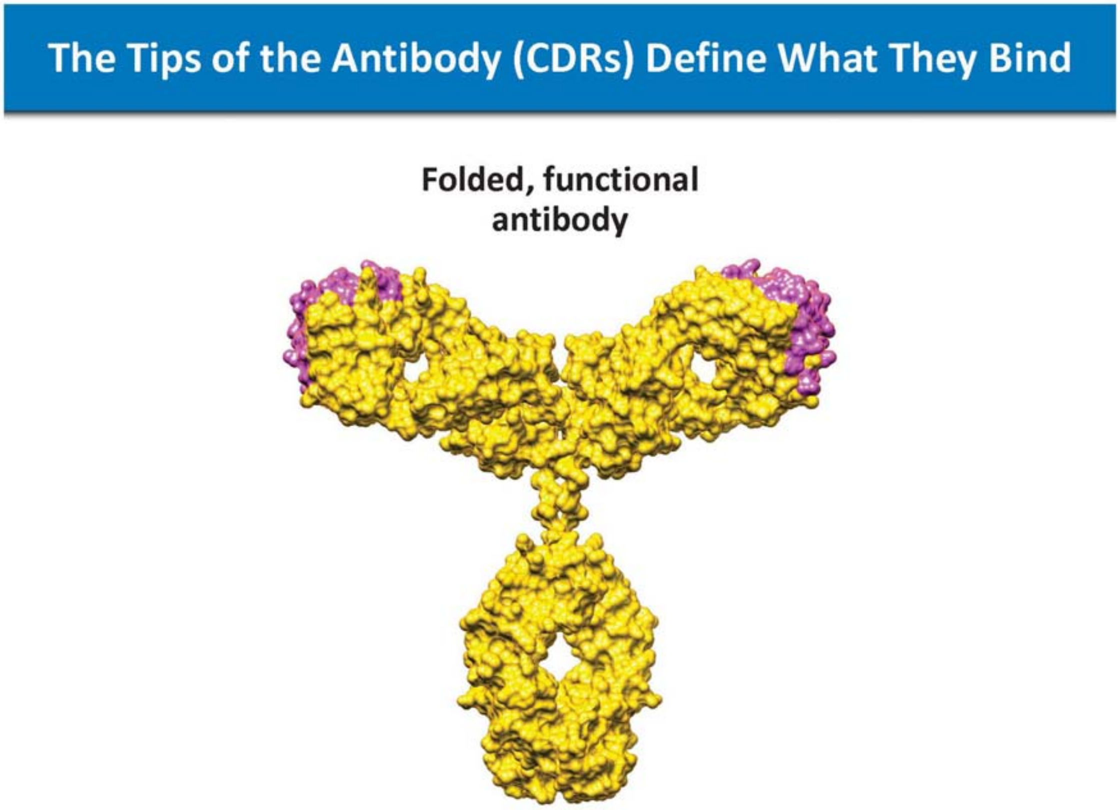
COUNTERSTATEMENT OF FACTS

I. Technological Background

A. Antibody Science

Antibodies are proteins that bind to and neutralize undesirable substances in the body. *See* Appx1257(614:17-20). An "antigen" is a "molecule or a portion of a molecule" to which an antibody binds. Appx332(36:39-42); Appx1335(922:5-15). Like all proteins, antibodies are made of chains of amino acids linked together by peptide bonds. Appx1257(615:10-15). The amino acid residues in a polypeptide chain interact with each other and cause the antibody to twist and fold, resulting in a three-dimensional structure. *E.g.*, Appx1259(620:10-13).

The structure of antibodies is well understood. Appx39. Antibodies have a characteristic Y-shaped structure with constant and variable regions. *Id.*; Appx331(33:6-11, 34:27-29); Appx1258(619:1-9). The graphic below depicts a typical antibody:


The Tips of the Antibody (CDRs) Define What They Bind
Folded, functional
antibody

The structure shown in yellow includes the constant region and the framework of the variable region. These structures are known and are highly consistent across all antibodies. Appx39; Appx331(33:1-11). In contrast, the magenta colored structures on the ends, known as complementarity determining regions ("CDRs"), vary from antibody to antibody and determine the antigen to which the antibody binds. Appx39; Appx331(33:28-33); Appx1302(791:5-9).

For an antibody to bind to an antigen, it must have both structural and chemical complementarity with the amino acids on the target antigen in three-dimensional space. *See*, *e.g.*, Appx1332(908:20-24); Appx1250-1251(587:20-588:8). When an antibody and antigen bind or "dock" together, non-covalent interactions form across the binding interface. Appx54-55; Appx57.

B. Amgen's Invention

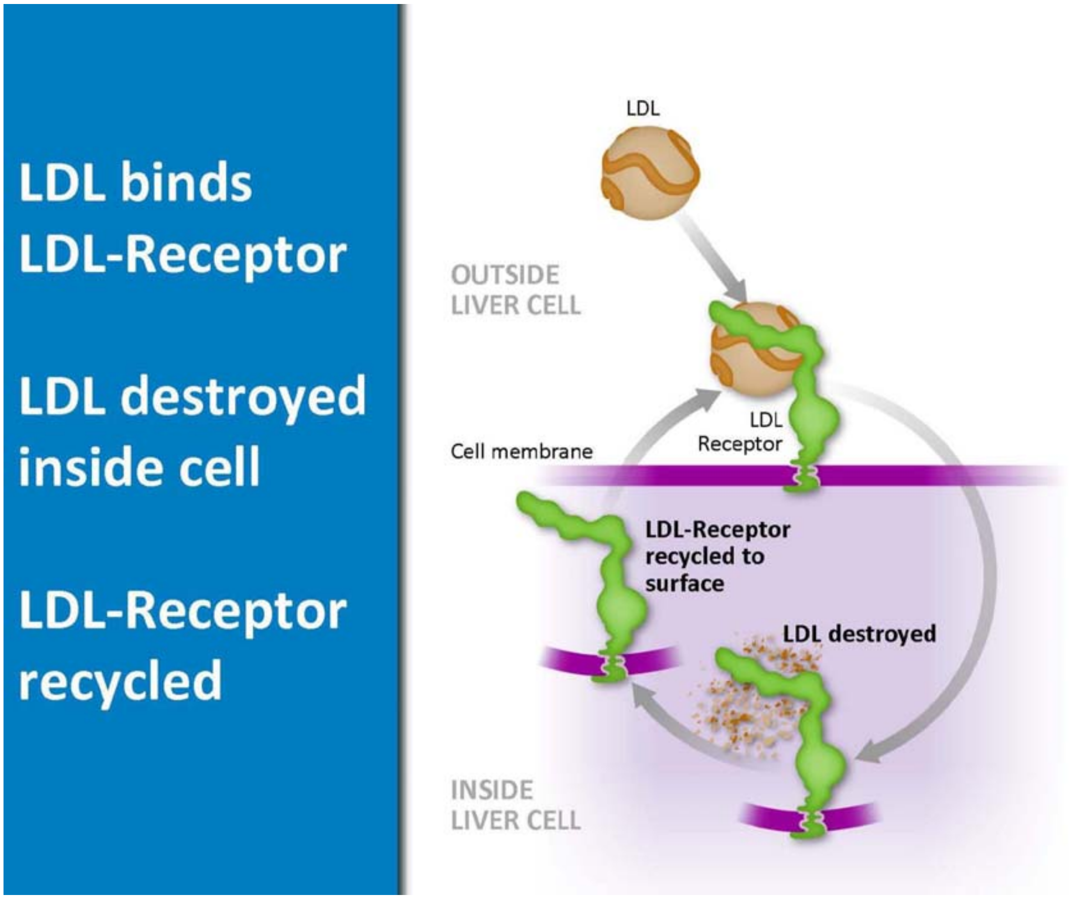
Amgen scientists were the first to invent antibodies that dramatically lower the level of bad cholesterol ("LDL-C") in the blood. *See* Appx29; Appx528-529; Appx913-914. Dr. Jackson of Amgen began studying the protein PCSK9 in early 2005. Appx1164(248:1-3). Researchers in the field knew that PCSK9 had a "link" to LDL-C levels, but no one knew how; "the steps in between were unknown." Appx1164(248:4-8). PCSK9 was understood to be a member of a protein family having protease activity—the ability to chew up other proteins—making it a potential target for small-molecule drugs.[1] Appx1164(248:10-249:2). After a "long time" of "frustrating" research

[1] In 2007, Sanofi also tried a small-molecule approach and failed. Appx1194(366:10-22).

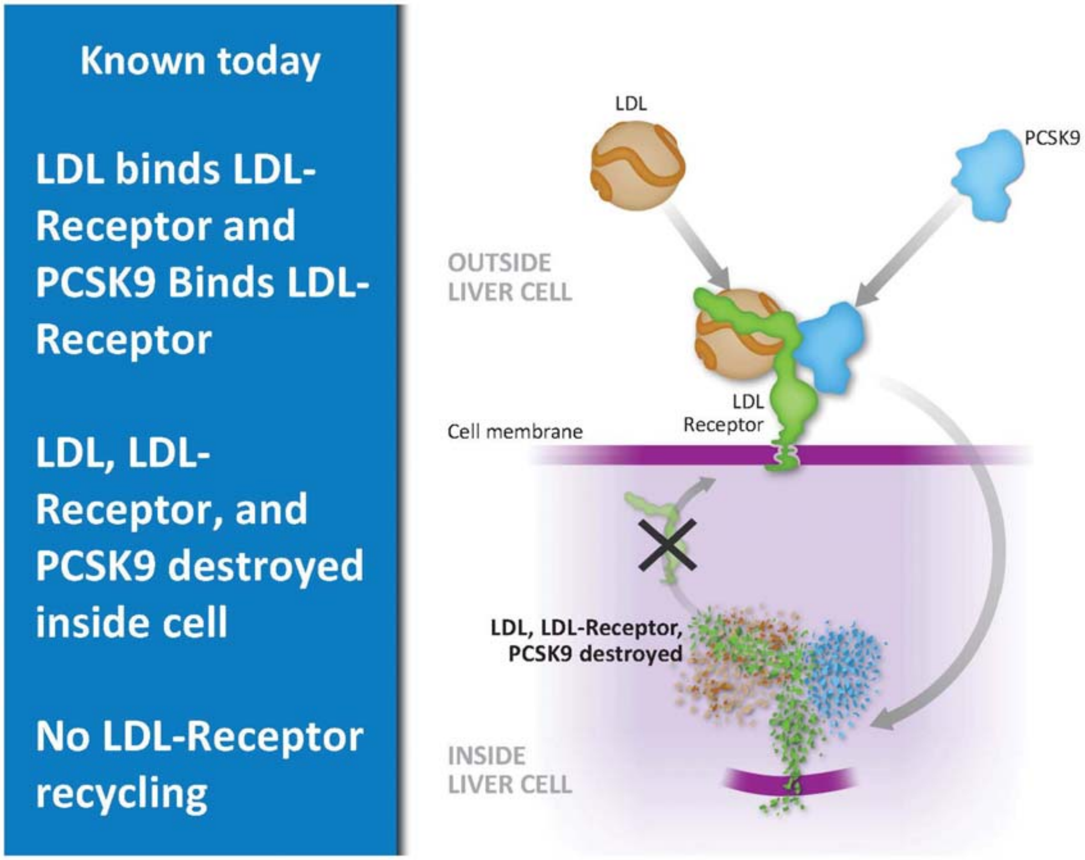
down this and other paths, Dr. Jackson "started to think of what alternative or unusual ways PCSK9 might be affecting" LDL-C. Appx1165(250:3-10).

In early 2006, Dr. Jackson and his team made the "surprising" discovery that PCSK9 binds directly to LDL receptors ("LDLR"), Appx1165(250:17-24), *i.e.*, without an intermediary, a result that was "unprecedented for that family of proteins." Appx1165(253:5-14). In June 2006, Dr. Jackson hypothesized that Amgen might be able "to generate an antibody that would bind to a specific region of PCSK9 that was making that interaction with the LDL receptor." Appx1167(258:19-24). He thought that such antibodies might thereby block the interaction between PCSK9 and LDLR, possibly lowering LDL-C in the blood. Appx1166(256:6-12); Appx1167(258:3-24); Appx4854.

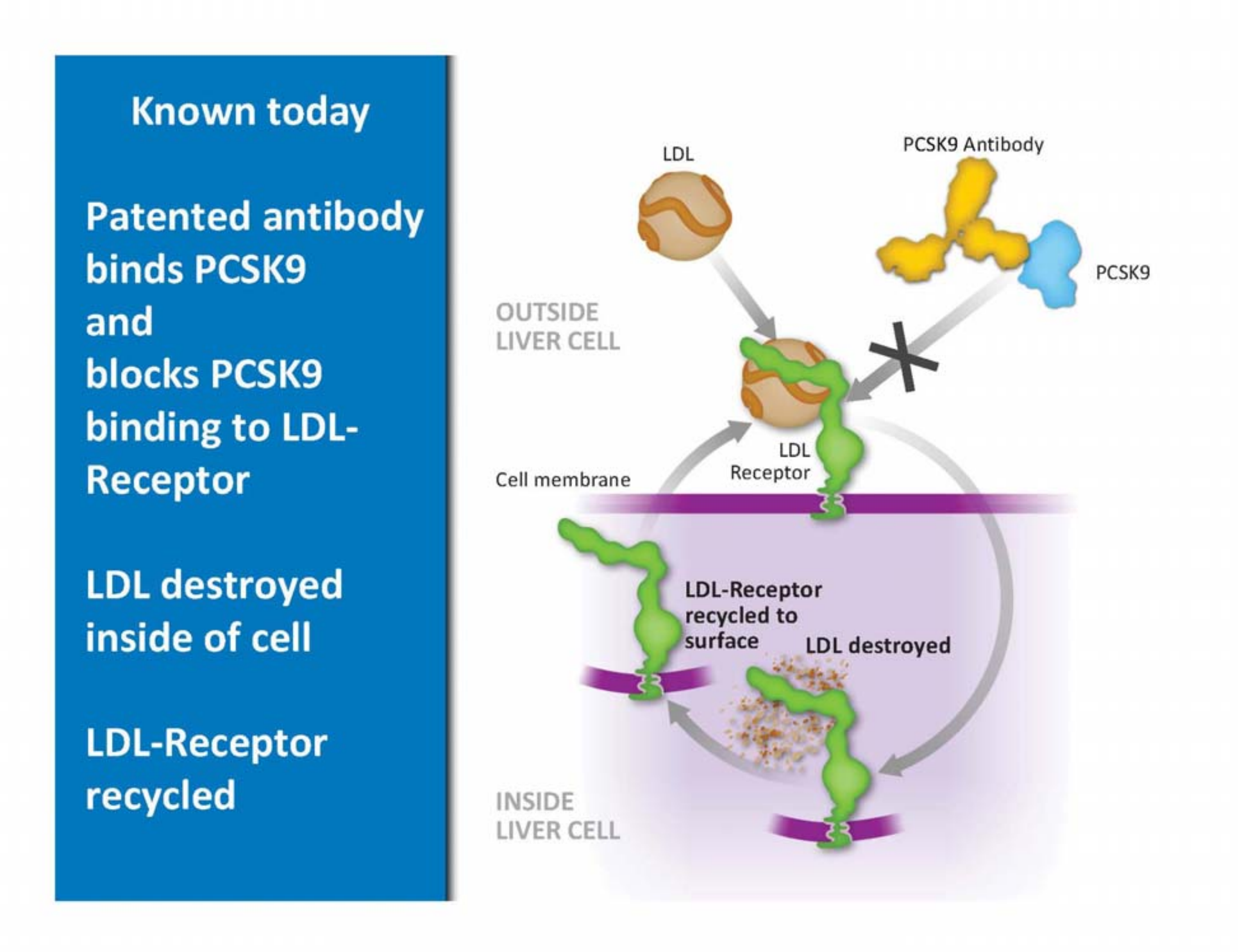
LDLR sits on the surface of liver cells and removes LDL-C from the bloodstream. Appx1163(242:23-243:8). When LDLR binds to LDL-C, the resulting complex is taken into a liver cell, where the LDL-C is destroyed. *Id.* LDLR then recycles to the cell surface to capture more LDL-C as shown in the figure below, *id.*:


LDL binds
LDL-Receptor
LDL destroyed
inside cell
LDL-Receptor
recycled
LDL
OUTSIDE
LIVER CELL
LDL
Receptor
Cell membrane
LDL-Receptor
recycled to
surface
LDL destroyed
INSIDE
LIVER CELL

We know today that when PCSK9 binds to LDLR, the liver cells destroy both the LDL-C and the LDLR, instead of allowing the LDLR to recycle to the surface and remove more LDL-C, Appx1163(243:11-18):


Known today
LDL binds LDL-Receptor and PCSK9 Binds LDL-Receptor
LDL, LDL-Receptor, and PCSK9 destroyed inside cell
No LDL-Receptor recycling
LDL
PCSK9
OUTSIDE LIVER CELL
LDL Receptor
Cell membrane
LDL, LDL-Receptor, PCSK9 destroyed
INSIDE LIVER CELL

Dr. Jackson's hypothesis was that an antibody binding to the small region on PCSK9 where LDLR binds could block PCSK9 from binding to LDLR, which would result in LDLR recycling and removing more LDL-C from the bloodstream, Appx1163(244:2-10):


Known today
Patented antibody binds PCSK9 and blocks PCSK9 binding to LDL-Receptor
LDL destroyed inside of cell
LDL-Receptor recycled
LDL
PCSK9 Antibody
PCSK9
OUTSIDE LIVER CELL
LDL Receptor
Cell membrane
LDL-Receptor recycled to surface
LDL destroyed
INSIDE LIVER CELL

In mid-2006, Amgen's inventors designed unique experimental approaches to give Amgen "the best chance" of generating and selecting antibodies that block the PCSK9-LDLR interaction. Appx1167(259:22-260:7). Amgen designed a "very specific immunization protocol," Appx1167(259:8-10), and specialized screening methods to detect antibodies that bind to PCSK9 and block LDLR, Appx1167(260:24-261:18); Appx1288(739:2-9); *see also* Appx351-355(73:34-81:34) (Examples 1-3).

By October 23, 2006—a full year before Regeneron's initial decision even to pursue a PCSK9 project, Appx2410(366:1-4)—Amgen created and identified three thousand monoclonal antibodies that bind to PCSK9. Appx48; Appx1167(261:17-25); Appx353(77:34-78:37). Hundreds of those antibodies blocked the PCSK9-LDLR interaction "well." Appx48; Appx354(80:22-27); Appx1315(840:23-25). One-hundred of them blocked the interaction very strongly (by more than 90%). Appx48; Appx354(80:22-37); Appx1263(638:1-3).

Amgen scientists then performed extensive testing to further characterize some of these antibodies. Experiments confirmed that the antibodies reduced PCSK9's effect on LDLR and LDL-C *in vitro* and lowered serum cholesterol in mouse models. Appx1170(271:12-272:13); Appx1171(275:15-276:4); Appx359-364. "That meant we were really on the way to having a therapy." Appx1171(276:1-4). These results confirmed Dr. Jackson's original hypothesis from June 2006, *i.e.*, that antibodies that block the PCSK9-LDLR interaction could lower LDL-C. Appx1172(280:1-10).

Amgen also determined the amino-acid sequences of 24 strongly blocking antibodies. Appx1169(266:25-267:11); Appx168-207 (sequences). These studies showed the antibodies had "good diversity" with respect to amino-acid sequences and antibody gene usage. Appx1290(746:3-6); Appx54; Appx1290(744:5-746:7). For example, the variable region sequences of two of the antibodies (21B12, which became Repatha, and 1A12) are more than 50% different. Appx1276(691:3-18); Appx1162(241:19-20).

In early 2007, Amgen performed "binning" studies, grouping antibodies into "bins" based on the location where they bind to PCSK9. Appx1169(267:16-23); Appx358-359(88:30-89:37). Antibodies that "bin" together bind to the same or overlapping regions on the target molecule. Appx40 n.4; Appx1169(267:19-268:25). The binning tests showed that the 24 strong blockers grouped into two bins, with antibodies 21B12 and 31H4 representing those distinct bins and not competing with each other. Appx1169-1170(269:1-270:10).

Amgen disclosed all of the binding, blocking, binning, sequencing, and *in vitro* and animal testing data on its diverse set of antibodies in a 323-page provisional patent application filed on August 23, 2007. Appx1172-1173(281:6-283:1); Appx2617 (provisional application).

To further elucidate the region on PCSK9 to which its antibodies and LDLR bind, Amgen scientists performed x-ray crystallography. Appx1173(283:2-25). They created three key crystal structures—PCSK9 bound to (1) antibody 31H4 alone, (2) antibodies 21B12 and 31H4 together, and (3) the portion of LDLR that binds to PCSK9 (the so-called "EGFa domain"). Appx1173(285:11-21); Appx1174(286:2-287:3); Appx283-293(Figs.17-20); Appx364-368(Ex.28-35). The first two of those structures confirmed "that the antibodies were binding in a small region side by side on PCSK9" and identified the specific amino acids on PCSK9 to which 21B12 and 31H4 bound. Appx1173(285:11-23); Appx1175(291:17-25). The PCSK9-LDLR crystal structure provided atomic level detail on what became known as the "sweet spot"—the region on PCSK9 where LDLR binds—and revealed that it comprises only 15 out of PCSK9's 692 amino acids. Appx60; Appx48 n.6; Appx364(100:5-10); Appx379 col.129 ("LENGTH: 692"); Appx1301(784:15-19).

Amgen filed these data in a second, 351-page provisional application, Appx2940, and a third, 711-page provisional, Appx3291, on December 21, 2007, and January 9, 2008, respectively. Appx1174-

1175(289:15-291:14). Amgen's experts attested at trial that the experiments in the patent were "well-conceived," "cleverly designed," Appx1296(770:16-18), and "an impressive piece of scientific work," Appx1329(897:14-15).

C. FDA Approval of Repatha

The antibody identified as 21B12 in the patent became Amgen's Repatha product. Appx41; Appx1162(241:19-20). Over the next several years, Amgen tested Repatha in a series of clinical trials and filed for FDA approval in August 2014. *See* Appx1175(292:15-293:6), Appx2362(173:10-11). The FDA approved Repatha on August 27, 2015, to treat (i) patients who had dangerously high LDL-C levels despite taking maximally-tolerated doses of other medications like statins, and (ii) an additional population of patients with a severe inherited form of high cholesterol. Appx2340(87:15-24); Appx2342(96:7-11); Appx2260-2293. The FDA approved a 140mg dose administered every two weeks and a 420mg dose administered once monthly. Appx2260-2261. In approving Repatha, the FDA considered evidence analyzing patients with "low" levels of LDL-C (*i.e.*, levels below 25 mg/dL) and found no evidence of any increase in side effects and no indication or signal of any potential safety concern regarding low LDL-C levels. Appx2264-2265; Appx2299-2301; Appx2343(97:8-98:7); Appx2345(105:19-106:13); Appx2346(109:3-9); Appx6202-6203; Appx6405-6406.

II. Amgen's Patents

The two patents, U.S. Patents Nos. 8,829,165 ("the '165 patent") and 8,859,741 ("the '741 patent"), share a common specification[2] and disclose and claim monoclonal antibodies that (i) bind to the sweet spot on PCSK9 and (ii) block PCSK9 from binding to LDLR. *See generally* Appx153-537 ('165 patent); Appx538-923 ('741 Patent). The undisputed priority date of the patents is January 9, 2008, the filing date of Amgen's PROV3 application. Appx1576; Br.12.

Amgen asserted claims 2, 7, 9, 15, 19, and 29 of the '165 patent and claim 7 of the '741 patent. Dependent claim 19 of the '165 patent is representative:

> 1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: *S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381* of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

[2] This brief cites to the '165 patent specification.

> 19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues *S153, I154, P155, R194, D238, A239, I369, S372, D374*, *C375, T377, C378, F379, V380, or S381* of PCSK9 listed in SEQ ID NO:3

Appx528(427:47-53); Appx529(429:7-12). The italicized letters and numbers designate the 15 amino acids forming the "sweet spot" provided by the PCSK9-LDLR crystal structure data. Appx364(100:5-10); Appx1314(836:1-4). The claims only cover antibodies that bind to one or more of the specific residues in the "sweet spot." *See id.*

The claims recite structure for the claimed antibodies. Monoclonal antibodies have the basic Y-shaped structure displayed above with all of the yellow region being well known and understood. Appx1239(543:7-14); Appx331(33:1-11). The CDRs of the claimed antibodies, the magenta colored portions above, bind to at least one (or two) of the recited residues on PCSK9. *E.g.*, Appx528(427:47-53); Appx529(429:7-12); Appx1259 (620:14-19).

The claims are drawn to a narrow class of antibodies. Amgen's experts testified that "the scope of the claims is narrow because all we're dealing with is antibodies that bind to a rather small region on the surface of PCSK9," *i.e.*, only 15 out of over 600 total residues on PCSK9. Appx1340(940:9-15); Appx1346(964:2-3); Appx1302(790:3-5); Appx1353(995:6-997:15).

III. Defendants' Infringement

Regeneron first decided to explore antibodies targeting PCSK9 in September 2007. Appx1194(366:20-367:2); Appx2410(366:1-4). Defendants learned of Amgen's Patent Cooperation Treaty ("PCT") application shortly after it was published on February 27, 2009, and at the same time that Defendants decided to go forward with their development program. Appx2365(187:18-188:8); Appx2410(368:2-10). Amgen's published application included the full specification of the asserted patents as well as claims covering antibodies directed to specific residues on PCSK9. *See* Appx5521 (claims 1, 7, 8, 9); *see also* Appx2413(377:22-378:15).

By June 2009, Defendants knew they faced a "patent issue" if the "binding epitopes" of Praluent and Amgen's disclosed antibodies were "similar"—and Defendants then confirmed that the epitopes did indeed overlap. Appx2366-2367(190:25-193:24).

Defendants nonetheless continued development of Praluent. After Amgen's patents issued and Amgen filed this lawsuit, Defendants filed for FDA approval of Praluent in November 2014 and used a priority review voucher purchased for $67.5 million that allowed them to leap-frog ahead of Amgen in the FDA review queue. Appx2362(173:16-174:20); Appx2412(375:10-17); Appx2294. FDA approved Praluent in July 2015, one month before Repatha. Appx2362(173:16-174:1); Appx5744. FDA approved Repatha and Praluent to treat the same class of patients, except that Repatha is approved for an additional population (persons with homozygous familial hypercholesterolemia) for which Praluent is not. Appx2340(86:14-87:5); *compare* Appx2261 *with* Appx2298.

With a jury trial scheduled only eight months away, Defendants rushed ahead and immediately launched Praluent at risk. Appx2378(237:8-12). Defendants touted their first-to-market status prominently in their marketing materials and on the Praluent website, Appx6453, and still do in their briefing, Br.8. They also "flooded the market with sample product to win patients immediately," before Amgen entered the market a month later. Appx2397(314:25-316:20);

Appx4519; Appx6429. Repatha competes head-to-head with Praluent in a two-player market, and payers and insurance companies have treated Repatha and Praluent as substitutable. *See* Appx2354-2355(144:20-145:8); Appx2374(221:17-224:5); Appx6456-6457.

IV. Procedural History

A. This Lawsuit

On October 17, 2014, eight months before Defendants' FDA approval, Amgen sued Defendants in the District of Delaware. Appx2464. The court encouraged—and both parties expressed a preference for—an accelerated schedule toward a trial on a full record in lieu of preliminary injunction proceedings. Appx939(16:11-13); Appx935-936(12:25-13:7); Appx939-940(16:25-17:4). Defendants stipulated to infringement, Appx996-997, leaving three invalidity defenses—written description, enablement, and obviousness—for trial.

B. Pre-trial Rulings

1. Exclusion of post-priority-date evidence

Before trial, each side moved to exclude the other from presenting post-January 2008 evidence for purposes of Defendants' written description and enablement defenses. Appx992. Although Defendants had stipulated to infringement, they sought to introduce evidence about

Praluent and other antibodies developed after the priority date of Amgen's patents to show that Amgen's disclosure was allegedly not representative of these antibodies. *Id.* Amgen intended to introduce evidence developed after the priority date showing the inherent characteristics of specific antibodies disclosed in the patents, to counter Defendants' assertions. *Id.*

After considering the parties' briefing and argument, the district court excluded all post-priority-date evidence. Appx994-995. Citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010), the court explained that written description is determined as of the priority date. Appx994. Recognizing that the court has "broad leeway…in terms of admitting evidence that illuminates the state of the art *at the time of filing* in order to determine whether there is sufficient disclosure of the claimed invention," the court exercised its discretion as the gatekeeper in determining whether "an expert's knowledge will help the jury understand the evidence." Appx994. Ultimately, the court concluded that "the clearest, most consistent result is to grant both motions and preclude the use of any [post-priority-date] evidence in connection with the issue of written description." Appx994-995.

Defendants moved for reconsideration. The court reaffirmed its earlier decision, Appx1030-1033, and stated that "this is an evidentiary question," Appx1001(9:23-24). Defendants urged the court to reconsider this issue repeatedly during trial. *E.g.*, Appx1154-1158(208:7-222:1); Appx1176(294:16-295:18); Appx1316(844:22-845:8). The court reiterated its ruling, explaining that Defendants' post-priority-date evidence would "only confus[e]" the jury. Appx1157(218:10-14). It also found that the evidence was "at best cumulative and at worst obliterating the line altogether," Appx1157(218:15-24), and Defendants "can prove [their case] without this post-priority date evidence." Appx1157(220:7-14).

2. Obviousness rulings

Amgen sought to exclude Defendants' expert testimony on obviousness because it relied solely on references that were not prior art. Appx2539. The expert relied on two PCT applications—Novartis (WO 2008/125623) and Schering (WO 2009/055783)—that were filed and published after the undisputed priority date of Amgen's patents. *Compare* Appx1963 & Appx2056 *with* Appx1576. Amgen argued that the PCT applications were not prior art under Section 102(e)(1) and not entitled to claim priority back to earlier provisional filings under 35 U.S.C. § 119(e) because Defendants failed to show the provisionals provided written description and enablement support for any claim of the PCT applications. Appx2538-2539.

The district court agreed with Amgen. Appx1034-1037. But instead of striking Defendants' expert testimony, the court postponed trial to allow Defendants "the opportunity to supplement their expert reports" to describe how the provisional applications provided support for the PCT applications. Appx1036-1037; Appx2604(4:11-21); Appx100 (3/4/2016 entry noting jury trial "rescheduled").

C. The Jury Trial

The court held a five-day jury trial on the patents' validity in March 2015. After the close of Defendants' case, Amgen moved for JMOL. Appx1285(725:20-726:6). Defendants did not. On obviousness, Amgen argued that Defendants failed to offer any evidence that the provisional applications qualified as prior art per the court's pre-trial ruling. Appx1374-1376. The court agreed and granted JMOL on obviousness. Appx1405(1076:21-1077:4). After hearing extensive fact and expert evidence on written description and enablement, the jury returned a unanimous verdict for Amgen, finding all of the asserted claims valid. Appx1586-1588.

D. The Post-Trial Orders

1. Denial of JMOL

Although Defendants failed to move for JMOL during trial, the court addressed their post-trial motion and determined that "substantial evidence supports the jury's verdict." Appx61. The court found that "[t]he parties and their experts largely agreed what the specification discloses—a screening process used to select 384 antibodies which blocked PCSK9 'well' … a certain subset of antibodies that blocked PCSK9 at over 90%; two antibodies (21B12 and 31H4), which underwent X-ray crystallography analysis; [and] a binding region of PCSK9 of fifteen residues that is the target of such antibodies." Appx59-60. The court found that the "parties' experts also agreed that the art discloses the research techniques necessary to perform antibody development and screening." Appx60.

Although Defendants' "experts focused on the 'middle' portion of the binding region and concluded that insufficient data and examples were disclosed in the specification," Amgen's "experts argued the opposite, that is, the examples and disclosures in the patent sufficiently described two antibodies which bind to a large portion of the binding region." Appx60. As the court recognized, "[a]n antibody that would bind to the part of the binding region that is not specifically bound by 21B12 and 31H4 is logically within reach using the disclosures of the specification (including the blocking and binning data)." *Id.*

After analyzing the competing evidence, and detailing Amgen's evidence for seven pages, the court stated that "Defendants' post-trial arguments essentially ask the court to reevaluate the experts' testimony and reach the opposition conclusion." Appx60. The court declined to do so, reasoning that the "jury is the finder of fact and is tasked with weighing the evidence and credibility of the witnesses." *Id.* Because the "parties' experts provided the jury with competing testimony on the interpretation of the data available in the specification," *id.*, the jury was entitled to "credit[] [Amgen's] testimony over that of [D]efendants' experts," Appx61, and "conclude[] that the asserted claims were not invalid for lack of written description or enablement," Appx60. Viewing the record in the light most favorable to

Amgen, the court found that "substantial evidence supports the jury's verdict." Appx61.

2. Denial of a new trial

The district court recognized that Defendants' new trial motions were "essentially request[ing] reconsideration" of earlier rulings, and the court declined to reconsider those rulings. Appx62-63. On the exclusion of post-priority-date evidence, the court stated: "the complexity of the matter mandated that the court draw lines and stick to them." Appx63. The court provided opportunity for argument and briefing on all of the issues and fully considered Defendants' arguments: "the court did not arrive at any of these positions lightly; indeed, it considered fulsome arguments and briefing." *Id.* With respect to JMOL on obviousness, the court noted that it "considered defendants' arguments … both before and during trial." *Id.*

3. Granting of a permanent injunction

Following the jury verdict, the court held a two-day evidentiary hearing on Amgen's motion for permanent injunctive relief. Appx29. Each side presented seven witnesses. After due consideration, the court exercised its equitable discretion by granting Amgen's motion. Appx28-

34. The court evaluated each of the factors from *eBay v. MercExchange, L.L.C.*, 547 U.S. 388, 394 (2006), finding two factors in Amgen's favor, one neutral, and one in Defendants' favor. Appx28-34.

The court found that Amgen was being irreparably harmed by Defendants' infringement. Appx32. The court found "there is no dispute that both Repatha and Praluent are approved to lower LDL cholesterol in a select group of patients," making the parties "head-to-head competitors in a targeted and developing market." Appx31. The court acknowledged Defendants' market presence was "causing harm to [Amgen's] reputation as the innovator in the PCSK9 cholesterol-lowering medicine, and [D]efendants' marketing of Praluent as 'The First U.S. FDA-approved PCSK9 Inhibitor' compounds such harm." Appx32. The court found that there is no adequate remedy at law to compensate Amgen for Defendants' infringement. *Id.*

The court found the balance of the harms neutral in that both parties spent billions of dollars and over a decade of work bringing their respective products to market. Appx33.

The court found the public interest factor to be a close call—putting the court "between a rock and a hard place"—due to two competing interests: "the traditional notions of being a patent holder and verdict winner" entitled to exercise exclusive rights against a direct competitor; and the court's view that "[t]he public generally is better served by having a choice in available treatments." *Id.* The court found that Praluent and Repatha are safe and effective to treat the same patient population, regardless of the difference in doses, and declined to accept Defendants' argument that Praluent's "low dose" is better for patients: "[t]he court will not substitute its judgment for that of the FDA, nor delve into weighing testimony on the propriety of treating patients with the 75 mg dose of Praluent." *Id.* The court weighed this factor in favor of Defendants due to the "public interest of having a choice of drugs." Appx33-34.

In concluding, the court weighed the equitable factors—with two in Amgen's favor and one in Defendants'—and exercised its discretion to enter the injunction. Appx34.

This Court granted Defendants' motion to stay the injunction pending appeal. DE59.

SUMMARY OF ARGUMENT

Defendants fail to meet their heavy burden of showing the trial court abused its discretion or made any errors that require reversal of the jury verdict or injunction.

I. Defendants fail to show an abuse of discretion in the court's exclusion of post-priority-date evidence. Trial courts have broad discretion in excluding evidence that is irrelevant, duplicative or confusing to the jury, and Defendants' proffered evidence was all three. Written description depends on the state of the art at the time of the invention, not later developments.

II. The court's jury instruction on "newly-characterized antigen" was taken directly from this Court's decisions. As this Court has recognized, antibodies have a "structure-function" relationship with their antigens. This relationship is sufficient to adequately describe claims to antibodies when the patentee has described in detail a newly-characterized antigen and the patent disclosure and the art make the production of such antibodies routine.

III. The court properly granted JMOL on Defendants' obviousness defense because Defendants failed to establish the two PCT applications were entitled to claim priority back to earlier provisional filings. Defendants did not even try to show that the provisionals provided written description and enablement support for the inventions claimed in the PCT applications, as required by statute.

IV. Defendants seek outright reversal of the jury verdict and JMOL on their Section 112 defenses without even applying the correct legal standards. First, Defendants waived this position by failing to move for JMOL at trial. Second, Defendants cite their own evidence while ignoring most of Amgen's, asking this Court to retry the facts. But the record was brimming with evidence of the depth and breadth of Amgen's patent disclosure; "substantial evidence" supported the jury verdict.

V. The court properly granted the injunction to end Defendants' ongoing and harmful infringement. Defendants cannot show an abuse of the court's discretion in weighing the evidence and balancing the relevant factors.

ARGUMENT

I. Defendants Are Not Entitled To A New Trial.

Having lost at trial, Defendants want a do-over. However, they point to no abuse of discretion or legal error that justifies giving them a second chance.

A. The Court Did Not Abuse Its Discretion In Excluding Post-Priority-Date Evidence.

Defendants complain loudly that the court abused its discretion in excluding their post-priority-date evidence. They ask, how could evidence of the accused product be kept from the jury? Answer—once Defendants admitted infringement, their product became irrelevant to the issues tried. The court excluded this evidence because (1) written description and enablement are determined as of the priority date and (2) it would have been cumulative and confusing. *See* Appx994-995; Appx1001(6:23-8:8); Appx1001-1002(8:23-10:6); Appx1157(218:10-20; 220:7-14).

As the court noted, it has wide latitude in determining whether post-priority-date evidence will illuminate the state of the art as of the priority date and "considerable leeway" in determining whether expert testimony will "help the jury understand the evidence and determine issues of fact." Appx994. This Court reviews exclusion of evidence only for abuse of discretion. *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1284 (Fed. Cir. 2011). There was none here.

1. The evidence was irrelevant.

Written description and enablement are judged at the time of filing. *E.g., Ariad*, 598 F.3d at 1355. Thus, post-priority-date evidence may be relevant only if it illuminates the state of the art at the filing date. *E.g.*, *In re Koller*, 613 F.2d 819, 825 (C.C.P.A. 1980); *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977). Because Defendants' antibody and the others they sought to introduce at trial did not exist at the filing date, they are not part of the state of the art at the filing date and therefore cannot "illuminate" it.

Defendants rely heavily on this Court's decision in *AbbVie*, 759 F.3d at 1285, calling the court's exclusion ruling "foreclosed by *AbbVie*." Br.20. But the *AbbVie* Court did not even opine on the admissibility of post-priority-date evidence, much less overrule the *Hogan* line of cases. In fact, the *AbbVie* parties did not raise that issue on appeal. And for good reason: the accused product came before, not after, the priority date. *Abbott GMBH & Co., KG v. Centocor Ortho Biotech Inc.*, 870 F. Supp. 2d 206, 218 (D. Mass. 2012). This Court simply affirmed the verdict based on the (unchallenged) record evidence. *See AbbVie*, 759 F.3d at 1298.

No case holds that post-priority-date evidence or evidence of the accused product is always admissible for Section 112 issues as a matter of law. In *U.S. Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1250-52 (1989), this Court found differences between the later developed accused product and the embodiments in the patent to be immaterial to Section 112. *See also Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1331-32 (Fed. Cir. 2003). *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.* confirms that such evidence is relevant only to show "the state of the art existing" at the time of the invention. 315 F.3d 1335, 1343-44 (Fed. Cir. 2003).

In *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1260-61 (Fed. Cir. 2004), an anticipation dispute involving a claim to priority back to the mid-1980s, this Court affirmed an evidentiary ruling admitting evidence showing that technology to make the claimed antibodies was too "nascent"—*i.e.*, was not yet part of the state of the art—as of the priority date. Here, Defendants' evidence had nothing to do with the technology being "nascent," and the experts agreed that antibody technology was well established and routine at the priority date. *See e.g.*, Appx50-51; Appx1204-1205(409:4-410:3); Appx1340(940:16-941:12.)

Defendants argue that *Hogan* did not address "post-priority evidence on the *scope of the claims*." Br.31-32. But Defendants' evidence had nothing to do with claim scope. As the district court recognized, Defendants did not raise it during claim construction, and they have not appealed claim construction. Appx1033 n.3.

Defendants assert that the written-description requirement "necessarily require[s] a comparison" between Amgen's disclosed antibodies and subsequently-developed antibodies. Br.25. Not so. The representative species test requires sufficient species to adequately represent the genus, *not* a specific description of every species within the genus, as Defendants argue. *In re Wallach*, 378 F.3d 1330, 1334 (Fed. Cir. 2004).

The law "does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention"—a requirement that would be "impossible" to satisfy. *SRI*

Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc); *accord Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). "[P]atent applicants have some flexibility" in how they comply. *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 928 (Fed. Cir. 2004). And the disclosure need not be "greater than that which is reasonable, having due regard to the subject matter involved." *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005).

2. The evidence would have confused the jury.

Defendants scarcely acknowledge the court's second basis for excluding this evidence—that it would be confusing and cumulative. Appx1157(218:9-24); *see also* Appx994-995.

Even if the evidence were relevant, as the court explained, this is ultimately "an evidentiary question, not [a] general question" of Section 112 law. Appx1001-1002(9:23-10:6). Courts may exclude relevant evidence, including expert testimony, to prevent "unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence." Fed. R. Evid. 403; *Egan v.*

Del. River Port Auth., — F.3d —, 2017 WL 1055568 at *8 (3d Cir. 2017). Federal Rule of Evidence 702 likewise permits courts to exclude expert testimony that would "overwhelm, confuse, or mislead the jury." *United States v. Downing*, 753 F.2d 1224, 1237 (3d Cir. 1985).

Such a ruling "is accorded particular deference, and … may not be reversed unless the determination is arbitrary and irrational." *Siemens*, 637 F.3d at 1284. The trial court is in by far "the best position to assess the extent of the prejudice caused a party by a piece of evidence." *United States v. Long*, 574 F.2d 761, 767 (3d Cir. 1978).

Although Defendants assert that the court repeatedly second-guessed itself, it was only entertaining Defendants' repeated requests for reconsideration. *See*, *e.g.*, Appx1154(208:6-22); Appx1176(294:16-295:10). The court held to its line and steadfastly concluded that Defendants' evidence would be "confusing," "at best cumulative," and that Defendants could "prove [their case] without this post-priority evidence." Appx1157(218:12-20; 220:7-14); *see also* Appx63; Appx1179(307:5-13); Appx1318(853:14-854:8).

The court knew that its standard written-description jury instruction included the following principle articulated in this Court's decisions, which are discussed above: "The specifications need not describe every species in a genus in order to meet the written description requirement." Appx1579. Defendants did not object to this jury instruction.

The court also knew that Defendants intended to argue just the opposite to the jury—that the claims were invalid because the patents did not disclose an antibody like Praluent. This would have been very confusing, as the jury may have concluded that Amgen had a duty to describe Praluent for its patents to be valid. The court excluded this evidence to "make sure … that the likelihood that it will be used for the wrong reason is reduced." Appx1001(9:15-20).

The court's ruling did not require Defendants to prove lack of representative species or enablement with "nothing," as they now assert. Br.27; *see also* Appx1157(221:3-13). Defendants presented the arguments at trial, supported by expert testimony, that they now assert they were precluded from making. The court explained that Defendants' "experts have looked at the patent, have looked at the representative species and have said, there is an absence." Appx1157(220:11-14). Those experts testified that the claims covered a wide range of antibodies with different sequences, including so-called "middle binders" and antibodies that bound to PCSK9 with a variety of chemical bonds, and in their view the specification failed to provide an adequate written description or enabling disclosure of such antibodies. Appx49-52. Defendants' counsel discussed these points repeatedly and at length in closing. Appx1425(1155:19-1156:6; 1156:23-1157:13), Appx1438(1207:23-1208:18).

Moreover, the district court excluded post-priority-date evidence from *both* sides. Amgen's excluded evidence would have shown that the patents disclosed more of what Defendants argued was missing. Appx1154-1155(208:15-210:11); Appx1156(215:21-217:14); Appx1317 (848:12-849:12). As but one example, later-performed x-ray crystallography demonstrated that 1A12, an antibody disclosed by amino-acid sequence in the patent's priority specification, was a "middle binder." *See* Appx2546-2548; Appx2557-2560.[3]

The court's evenhanded case-management decision was neither

[3] Defendants' characterization of Amgen's third generation research program as "still searching" for a middle binder is wrong. *See* Br.33. The purpose of that research was to develop a pH-sensitive antibody. Appx1154(208:15-22); Appx1229-1230(503:12-505:5).

"irrational" nor "arbitrary," and thus not an abuse of discretion. *Siemens*, 637 F.3d at 1284. For the same reasons, any error would have been harmless. *See Abrams v. Lightolier Inc.*, 50 F.3d 1204, 1218 (3d Cir. 1995).

B. The Court Properly Instructed The Jury On The "Newly-Characterized Antigen" Test.

1. The instruction correctly stated the law.

Written description requires sufficient disclosure in the patent to convey to a person of skill in the art what is claimed and the inventor's possession of the claimed invention. *Ariad*, 598 F.3d at 1351. As discussed above, written description is not confined to any rigid formula in antibody or any technology. *See* p. 37, *supra.* For claims with functional language, a written description is adequate if it discloses "a correlation between structure and function." *Ariad* 598 F.3d at 1350.

As the court instructed the jury, the newly-characterized antigen test is one way of establishing a structure-function correlation in the context of antibodies:

> In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies

> at the time of filing was such that production of antibodies against such an antigen was conventional or routine.

Appx1580.

The court took that instruction directly from this Court's controlling precedents: "[A]s long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004). This standard applies to "disclosure of newly characterized antigens where creation of the claimed antibodies is routine." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011). This Court "adopt[ed]" the newly-characterized antigen test after being "persuaded" by the Patent and Trademark Office's guidance "on this point." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

Defendants' and *amici's* arguments that the court erred in giving this instruction are nothing but a disagreement with this Court's prior decisions. In *Noelle*, the Court recognized that it had "adopted" the newly-characterized antigen test in its "past precedent." 355 F.3d at

1349. The Court then applied the test: "[i]f Noelle had sufficiently described the … antigen, he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen." 355 F.3d at 1349. Defendants' footnote calling *Noelle* "[r]egrettabl[e]," Br.39 n.10, all but concedes their disagreement with this Court's binding precedent.

Inexplicably, Defendants and *amici* assert that the PTO has "withdrawn" the newly-characterized antigen test. *E.g.,* Br.37,41. But language nearly identical to the court's instruction is found in the MPEP, which cites *Centocor* for this very proposition. MPEP § 2163 ¶ II.A.3(a). Defendants and *amici* fixate on one set of prior training materials that were "archived" (not "withdrawn," as they argue), while misrepresenting that newer training materials omit the test, Br.41, when they actually include it. *See* U.S.P.T.O., *Antibody Decisions and Their Compliance with the Written Description Requirement,* [ARCHIVED] (http://bit.ly/2kLrTLa); U.S.P.T.O., Powerpoint of 10/7/2015 CBT at slide 17, (http://bit.ly/2nMsWPU). The Patent Trials and Appeals Board consistently applies the test to antibody claims. *E.g., In re Bicknell*, Appx6498-6501 (PTAB Jan. 8, 2016).

Lacking legal authority, Defendants turn to an article written by Eli Lilly patent attorneys. *See* Br.39-40. Lilly and Pfizer are partisans, not true *amici*. Lilly fails to disclose that it has a PCSK9 antibody therapy in clinical trials. *See* Lilly Development Pipeline (http://bit.ly/2nDxgko). Pfizer alleges it is not developing an anti-PCSK9 antibody "[a]t present," but expresses concern that its recently developed PCSK9 antibody bococizumab is covered by Amgen's patents. Pfizer Br.2, 4. Articles and self-interested *amicus* briefs are no match for this Court's controlling precedents.

2. The "newly-characterized antigen" test is sound.

A claim to an antibody that binds to a "fully characterized antigen" satisfies the structure-function test because of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *Noelle*, 355 F.3d at 1349 (quotation marks omitted); *accord Enzo*, 323 F.3d at 964.

Defendants and *amici* assert that conclusion is overreaching and contrary to the science. Br.41; Lilly Br.18. But once Amgen's scientists identified the sweet spot on PCSK9 in detail, determined that it was antigenic, and developed exemplary antibodies thereto, the advanced state of the antibody art and the disclosures in the patent made production of the claimed antibodies—including antibodies with widely diverse amino-acid sequences—a matter of routine. Appx1335(921:4-922:24); Appx1307-1308(811:21-812:3); *see Bicknell* at Appx6500. Rather than losing touch with the science, the test has become *more* important as production of diverse antibodies to a given antigen has become all the more routine. *Id.*; Appx1334(919:25-921:10), Appx1340(940:16-942:3).

Defendants argue that describing a target does not describe an arrow. Br.35-36. But there are different ways of disclosing inventions, *see* p. 37, *supra,* and the application of the written-description requirement "will necessarily vary depending on the context." *Ariad*, 598 F.3d at 1351. As *Noelle* stated, because antibodies have "well-defined" structural and functional characteristics and the technology is so mature, specifically characterizing the antigen does demonstrate possession of antibodies that bind to the antigen where, as here, production of the relevant antibodies would be routine. *See, e.g.,* Appx1314(837:24-838:4); Appx1335(921:11-20; 922:13-24); Appx1301

(784:9-19); Appx1313-1314(835:18-836:21).

While Defendants and *amici* urge that antibody claims should be limited to amino-acid sequences of the exemplified antibodies, the power of antibody technology to readily make additional antibodies having different sequences renders such claims meaningless to keep out followers like Defendants and *amici* Pfizer and Lilly that add nothing to the advance of science. Thus, antibody claims that provide protection beyond the specific embodiments are "necessary to adequately protect [the] invention from copyists who could otherwise make a minor change to the sequence and thereby avoid infringement while still exploiting the benefits of [the] invention." *Enzo*, 323 F.3d at 966.

3. The wording of the instruction was not in error.

Defendants contend that the court's instruction should have stated that the test applies only if the patent claims "both the protein and an antibody that binds to it." Br.42 (quoting *Centocor*, 636 F.3d at 1351-52). But this argument is based entirely on an out-of-context phrase in *Centocor*. That case goes on to confirm that the test governs a "claim [to] an antibody," not a claim to an antigen or a claim to both. 636 F.3d at 1352. Indeed, *Centocor* found the test was not satisfied there because "generating the claimed antibodies was not routine" at the priority date, Br.40, not because the claims failed to include the antigen. 636 F.3d at 1352-53. Defendants' position makes no sense because antigens are typically naturally occurring proteins that are ineligible for patenting under Section 101. *See Ass'n for Molecular Pathology v. Myriad Genetics*, 133 S.Ct. 2107, 2111 (2013). There is no reason to require antibody claims to recite additional and typically ineligible subject matter.[4]

Defendants also assert that the instruction erroneously omitted a single word—"claimed." Br.42-43. Defendants waived that nitpick by not raising it in the district court. *See* Appx1465-1467; Fed. R. Civ. P. 51; *Alexander v. Riga*, 208 F.3d 419, 426 (3d Cir. 2000).

Moreover, courts enjoy "considerable discretion" in formulating jury instructions, *Boyle v. United States*, 556 U.S. 938, 946 (2009), which must be read "in the context of the instructions as a whole and the trial record," *Estelle v. McGuire*, 502 U.S. 62, 72 (1991). The instruction refers to "production of antibodies against such an antigen." Appx1580. In context, the instruction can only be read to refer to "production" of the claimed antibodies. *See*, *e.g.*, Appx1297(772:2-10). Defendants point to nothing that suggests a different understanding at trial. Thus, the instruction was not erroneous, and any error in its wording would have been harmless. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 638, 642 (Fed. Cir. 2011).

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[4] Lilly argues that the court wrongly applied the test to claims that include not only a binding limitation but also a blocking limitation. But blocking LDLR is a further *limitation* on the claims, not an *"expan[sion]"* of them, as Lilly contends (at 16).

4. Any error was harmless

The newly-characterized antigen instruction could not have changed the result because the claims were amply supported as a matter of law on alternative grounds—disclosure of representative species and common structural features—as discussed in Section II below. Indeed, as the district court noted, the test was not dispositive. Appx61. For that reason, any error was harmless. *Therasense Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1333-37 (Fed. Cir. 2010).

C. The Court Properly Granted JMOL Of Non-Obviousness.

The court properly granted JMOL of non-obviousness because Defendants failed to show that their references qualified as prior art under the statute. Defendants cited two PCT applications that were filed after the January 9, 2008, priority filing for Amgen's patent claims. Appx1963; Appx2056; Br.13. As such, the PCT applications are not prior art under Section 102(e)(1). And Defendants failed to show that either PCT was entitled to reach back to provisional filings in order to pre-date Amgen's priority filing.

It is undisputed that provisional filings are not themselves prior art under Section 102(e)(1) because they are not applications "published under Section 122(b)." *See* 35 U.S.C. §§102(e)(1) (2006); & 122(b)(2)(a)(iii) (2006). Under the patent statute, the only way a later application can become prior art by claiming priority to an earlier provisional filing is under Section 119(e)(1), which requires a showing of compliance with Section 112, first paragraph—written description and enablement. *Dynamic Drinkware LLC v. Nat'l Graphics, Inc.,* 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Pre-AIA Section 119(e)(1) provides that "an application for a patent" is entitled to the priority date of a provisional only if the "invention [was] disclosed in the manner provided by the first paragraph of section 112 … in a provisional application." 35 U.S.C. § 119(e)(1) (2006). This Court has consistently construed that language to mean exactly what it says: "the specification of the *provisional* must 'contain a written description of the invention and the manner and process of making it, in such full, clear, concise, and exact terms,' 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application." *Drinkware,* 800 F.3d at 1378 (quoting *New Railhead Mfg. v. Vermeer Mfg.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002); *see also In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010).

Of course, it is "axiomatic" that the claims define the invention for this and other purposes. *In re Wertheim*, 646 F.2d 527, 537 (C.C.P.A. 1981). Thus, to be a basis for claiming priority, a provisional must provide written description and enabling support for at least one claim in the subsequent application. *Drinkware,* 800 F.3d at 1378, 1382.

Defendants elected not to even try to show written description and enablement in the provisionals, Appx1217(460:14-461:9); Appx1218 (462:4-19); Appx1232-1233(515:22-516:2), even after the court delayed trial to permit them to supplement an expert report. Appx1037; Appx2604(4:11-21); Appx100 (3/4/2016 entry noting jury trial "rescheduled"). Both provisionals were purely prophetic, Appx4002;

Appx4085, containing no disclosure of any monoclonal antibodies. *See, e.g.*, Appx1218(462:20-463:2); Appx1221(476:5-7). Given that Defendants were asserting that Amgen's disclosure of 24 antibodies was insufficient, they could not plausibly argue to the jury that the provisionals contained adequate written descriptions or an enabling disclosure.

Rather, Defendants attempt to limit the plain language of Section 119(e) to issued patents and not to applications. Br.46. But Section 119(e)(1) expressly applies to "[a]n application for patent." And it sets forth a single standard for establishing priority—not different standards depending on the purpose for which priority is sought. The same standard applies equally to Amgen in showing priority to its provisional and to Defendants in seeking to use later-filed applications as prior art. Under Defendants' approach, *Drinkware* would be a dead letter because litigants could always rely on a published application instead of the issued patent.

Defendants argue *Drinkware* incorrectly relied on *Wertheim's* concerns about "secret prior art," which they contend were effectively abrogated by amendments requiring publication of *utility applications*.

Br.47-48. But *Drinkware* was based on the statute, Section 119(e), and this case concerns a claim to priority to unpublished provisionals, not published utility applications. Allowing an application to claim priority back to an unpublished provisional that does *not* adequately disclose a subsequently-claimed invention would give patent rights to someone who was not the "first true inventor" of that invention. *Cf. Alexander Milburn v. Davis-Bournonville*, 46 S. Ct. 324, 399, 401 (1926) (allowing priority where prior application contained complete description of claimed invention and could have issued on day filed).

Defendants argue that *Drinkware* cannot apply to applications because claims may change during prosecution. Br.48. But Defendants' burden was to show support for a claim in the published applications they cited as prior art (the filed PCT applications), not for claims in subsequent prosecution or in any other subsequent filings that Defendants did not rely on as prior art. What happens in prosecution is irrelevant to whether an application is prior art under Section 102(e)(1).

Defendants' arguments regarding the stringency of the written description and enablement standards that apply to prior-art references are inapposite. Br.49-50. The question here is whether a patent application qualifies as prior art. The cases cited by Defendants relate to the effect of references, already established as prior art, on anticipation or obviousness. And Defendants' concerns regarding mini-trials are overblown: establishing a reference as prior art often involves "mini-trials" over, for example, whether the art was a printed publication, public use, or sale. *Cf.* 35 U.S.C. § 102(b).

Defendants argue there should be a presumption that applications are entitled to their provisional filing dates for whatever subject matter is disclosed therein. Br.51. But a presumption would be inappropriate because the PTO does not routinely examine priority applications for support. *Drinkware*, 800 F.3d at 1380.

Defendants argue for a lesser "carried forward" priority analysis. Br.51-52. To do so, Defendants would have this Court either (i) rewrite Section 102(e)(1) to include provisional applications as prior art for whatever they disclose, or (ii) hold that mere inclusion of the same language *ipsis verbis* in two filings allows the second to claim priority to the first. But Section 102(e)(1) expressly excludes provisionals under Section 122(b). And the mere inclusion of language *ipsis verbis* has long been held to be insufficient to meet the written description requirement.

Ariad, 598 F.3d at 1349; *New Railhead*, 298 F.3d at 1295-96. Even *Giacomini*, upon which Defendants rely, is to the contrary. It states "[a]n important limitation is that the provisional application must provide written description support for the claimed invention" in addition to the carried forward language. 612 F.3d at 1383.

Section 119(e) also requires compliance with Section 112's separate enablement requirement. Defendants provided no evidence that the provisionals enabled a single claim of their PCTs, further warranting the JMOL grant. Appx1217(460:19-22); Appx1218(462:4-8).

Finally, Defendants complain that they were surprised by the court's JMOL ruling and only given one page to brief the issue. Br.45. There was no surprise. The court had entered a ruling before trial, delayed the start of trial, heard argument at trial, and heard the expert's testimony on this issue. *See* pp. 24-25, *supra*; *see also* Appx1127(102:24-105:8); Appx1217(460-14-461:14); Appx1218(462:12-19). As the court stated, "the court fully considered defendants' arguments as to the applicability of the *Drinkware* case, both before and during trial." Appx63. The court granted JMOL at the usual time after

Defendants' evidence was presented. Appx1285(725:20-726:4); Appx1405(1076:21-1077:3).

II. Defendants Are Not Entitled To JMOL On Written Description Or Enablement.

A. Defendants Waived JMOL.

A party must move for JMOL "before the case is submitted to the jury" and "renew[]" that motion after the verdict. Fed. R. Civ. P. 50(a)-(b). After the court invited "placeholder" Rule 50(a) motions, Amgen sought JMOL. Defendants did not. Defendants thereby waived JMOL on the Section 112 issues. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 845 (Fed. Cir. 2010).

The court considered Defendants' JMOL motion because Amgen was "apprised during trial of defendants' allegations." Appx45. Defendants did not, however, move for JMOL before the case went to the jury. District courts have discretion to determine the *adequacy* of a Rule 50(a) motion, but no discretion to eliminate the requirement that such a motion be made. *See Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1106-07 (Fed. Cir. 2003) (reversing for this reason). The court did not determine that Defendants had taken any action—orally or in writing, formally or informally—that constituted a Rule 50(a) motion. *See* Appx44-45. If failing to take any such action were excused, Rule 50's requirement of a pre-verdict motion would be a dead letter, as would this Court's decision in *Duro-Last*. Consequently, Defendants waived JMOL.

B. Extensive Evidence Supports The Written-Description Verdict.

Even apart from waiver, Defendants' challenge to the sufficiency of the evidence is meritless. After reciting some of Amgen's evidence over seven pages in its opinion, the court concluded: "substantial evidence supports the jury's verdict." Appx61. In arguing for reversal, Defendants ignore Amgen's evidence and seek to rely on the (disputed) testimony of their experts. But written description is a question of fact, *Ariad*, 598 F.3d at 1351, that Defendants must prove by clear and convincing evidence, *e.g.*, *Enzo*, 323 F.3d at 962. Also, this Court must draw all factual inferences and credibility determinations in favor of the verdict, not in favor of Defendants' experts. *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003).

Defendants' challenges fail for another reason. The court instructed the jury that it could find written description on multiple grounds: representative species, common structural features, or newly-characterized antigen. Appx1579-1580. Defendants fail to show they should prevail on any one of those grounds, let alone all three as required to reverse the jury verdict. *See Cordance Corp. v. Amazon.com, Inc.*, 658 F.3d 1330, 1338–39 (Fed. Cir. 2011)*; Hofkin v. Provident Life & Acc. Ins. Co.*, 81 F.3d 365, 369 (3d Cir. 1996).

1. Representative species

Defendants and *amici* argue the patents disclose the amino-acid sequences of "only two" claimed antibodies, 21B12 and 31H4. Br.54. But the jury heard testimony that the patents disclose 24 antibodies, by their amino-acid sequences, that adequately represent the full scope of the claims. Appx55-57, Appx60. Amgen's evidence showed those antibodies bind across the entire "sweet spot" on PCSK9 *and* are quite diverse in amino-acid sequence. Appx1290(744:5-745:11); Appx1309(818:18-819:22); Appx1311(825:15-826:3); Appx1312-1313(831:16-832:3).

Defendants' apparent position is that Amgen did not conclusively prove that the other 22 antibodies bind to the sweet spot. That position is baseless and ignores the evidence. As the court recognized in denying

JMOL, Amgen witnesses testified that based on X-ray crystallography for 21B12 and 31H4, and the binning and blocking data for the 22 co-binning antibodies, the patents disclose 24 blocking antibodies that bind to the sweet spot. Appx56-57; Appx1339(937:24-938:6); Appx1310-1311(823:15-825:9); Appx1311-1312(827:6-828:9); Appx1312(829:9-14). Further, Defendants are trying to flip the burden of proof on its head: they bear that burden, not Amgen, and the jury was entitled to agree with Amgen's evidence.

Defendants contend that the 24 disclosed antibodies are not representative of the "structural variability" of the genus. Br.55. But the jury heard expert testimony that the 24 antibodies cover seven antibody gene families having "multiple heavy chain genes" and both kappa and lambda light chain genes, and have "quite an extensive [sequence] diversity." Appx1290(744:10-745:11); Appx1335-1336(923:7-926:7). The jury also heard evidence that the patent taught a person of skill even more species having different amino-acid sequences, through, for example, conservative amino acid substitutions, Appx1337(930:8-931:6), Appx1337-1338(931:10-932:13-25), CDR shuffling, Appx1338(933:8-934:8), or phage display, Appx1277(695:10-20).

Amgen's experts also testified that a skilled artisan would consider 21B12 and 31H4 alone to be fully representative of the claimed antibodies given the mature state of the art in light of the disclosure in the patent. Appx1307-1308(811:2-812:3); Appx1309(818:6-11). 21B12 and 31H4 cover the full expanse of the sweet spot "virtually perfectly" by binding to the inner- and outer-most regions of the sweet spot. Appx1306(806:15-21); *see also* Appx1245(565:1-8).

Fundamentally, "the disclosure of [the sweet spot] and examples of antibodies that are able to bind to [it]…tell the skilled person that the inventors know and are in possession of all the antibodies that can bind to here." Appx1335(922:16-20). "[T]he patent [] tells you how to generate antibodies that will inevitably recognize this region…." *Id.* (921:14-16.)

Defendants' arguments emphasizing their experts' testimony, while largely ignoring Amgen's experts' testimony, improperly ask the Court to reweigh the competing evidence and determine the credibility of the witnesses. But as the trial court stated: The "parties' experts provided the jury with competing testimony on the interpretation of the data available in the specification," and the jury was entitled to "credit[]

[Amgen's] testimony over that of [D]efendants' experts" and "conclude[] that the asserted claims were not invalid for lack of written description." Appx61.

In *Centocor*—the only antibody case in which this Court reversed a fact-finder's determination of adequate written description—the specification did "not describe a single antibody that satisfies the claim limitations." 636 F.3d at 1350-51. At the time of the application, "it was entirely possible that no … antibody existed that satisfied the claims." *Id.* at 1351; *see also Noelle*, 355 F.3d at 1349. In contrast, Amgen's patents provide a wealth of disclosure and at least 24 distinct, exemplary antibodies.

Defendants' reliance on *AbbVie* is likewise misplaced. There this Court affirmed the jury verdict and noted that all the examples were derived from a single source and "share[d] 90% or more sequence similarity." 759 F.3d at 1300. Here, the 24 distinct antibodies represent seven antibody gene families and "extensive" sequence diversity.

Defendants cannot save their case with a one-sentence assertion that the patents only exemplify *human* antibodies. Br.55. Defendants cite to *Lilly*, but cite no evidence. But there was evidence that the patent described and enabled whatever type of claimed antibody one desired, including other species. Appx1278-1278(697:9-699:14); Appx1340(940:16-941:5; 942:4-943:25); Appx329(30:25-27).

2. Common structural features

Amgen presented overwhelming evidence showing common structural features of the claimed antibodies that correlate to their binding and blocking functions. *See Ariad*, 598 F.3d at 1350. First, the jury heard from experts on both sides about numerous structural features that all antibodies have in common and which contribute to the antibodies' three-dimensional shape. Appx1195(371:8-17); Appx1239(543:7-25); Appx1258-1259(617:20-621:14); Appx1338(930:12-22); *see* Appx330-332(32:6-35:12). The three-dimensional structure allows scientists to understand and describe antibody-antigen interactions, which only occur in the CDR regions (the small tips of the Y-shaped structures). Appx1309(818:6-17); Appx1259(620:14-19) Appx1302-1303(791:10-792:17); Appx1330(901:21-902:10); *see also* p. 8, *supra*.

Amgen's experts explained how scientists have understood for decades that these interactions are dictated by concepts of "fit" and "shape complementarity." Appx1331(905:24-906:10); Appx1332(909:6-911:18); Appx1333(912:15-22); *see also* Appx1302(791:15-20). Experts on both sides agreed that antibodies that share the same binding site must necessarily "share structural features," Appx1332(908:20-24), that provide "chemical and physical complementarity to that region." Appx1250(587:20-23); *see also* Appx1242(555:4-556:3).

Dr. Rees explained that three-dimensional "structural features of the antibody lead, of course, to the functions of binding and blocking … you have to get close in and the two surfaces have to interact before you can have binding." Appx1333(912:8-22); *see also* Appx1300(783:25-784:19); Appx1314-1315(839:6-840:17). The experts testified that the asserted claims therefore include both structural and functional limitations, and there is a correlation between the claimed structural and functional features. Appx1314(838:8-13); Appx1332(908:20-24); Appx1333(912:8-22); Appx1339(937:5-10).

The jury also heard evidence that the common structural features allowed skilled persons to "visualize or recognize" the narrow class of claimed antibodies, even if they could not "write out" or "predict" the amino-acid sequences of the CDRs from scratch. Appx1314(836:5-838:4); Appx1332-1333(911:19-912:2). Amgen's expert testified that a "writing out" requirement has no meaning: "That isn't the way any scientist would go about studying antibodies." Appx1314(836:5-21); *see also* Appx1314-1315(839:13-840:14); Appx1332(908:10-24). Based on Amgen's disclosure of generating antibodies that bind to the "sweet spot" and block the PCSK9-LDLR interaction, a skilled person could "visualize antibodies you couldn't visualize before" and would understand the inventors possessed the full scope of claimed antibodies. Appx1314(837:9-14).

When Defendants refer to "structure" in their brief, they apparently mean only one thing: amino-acid sequence. But that is not the only way to describe biologics in patent claims. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Their contention that Amgen's expert Dr. Petsko admitted that "structure" cannot be predicted based on an antibody's binding site, Br.15, is a flagrant mischaracterization of his testimony. He was referring to amino-acid sequence, not structure. The context for that statement is his explanation that a scientist would *not* "go about studying antibodies" by writing out amino-acid sequences. Appx1314(836:5-21). To antibody scientists, what "matters" is the three-dimensional structure of a folded protein—a structure discerned primarily by examining where and how the antibody binds and whether it blocks the PCSK9-LDLR interaction, not by constructing its amino-acid sequence. *Id.;* Appx1309(818:6-17).

Defendants' complaint that Amgen's evidence of a structure-function correlation is "circular" ignores the science. Every claimed antibody has known constant and framework regions. Appx1239(543:7-25); Appx1258(618:1-619:9); Appx331(33:1-11). They also have both shape and chemical complementarity in the CDRs to bind residues in the sweet spot. *E.g.*, Appx1332(908:20-24). By disclosing the sweet spot in exacting detail, the patents disclose common structural features of the claimed antibodies—just as describing a piece in a three-dimensional jigsaw puzzle would describe the portion of another piece that must interlock with it. *See Rochester*, 358 F.3d at 925 (recognizing that, depending on the state of the art, "disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it”).

3. The “newly-characterized antigen” test

As discussed above, the newly-characterized-antigen test is one way of demonstrating a structure-function correlation. *See* Section I.B.2, *supra*. The jury heard more than sufficient evidence that the antigen was characterized in detail and that, given the patent disclosure, production of antibodies against the antigen was routine. Appx60.

The inventors newly characterized and elucidated the critical binding region of the PCSK9 protein and described it in great detail in the specification. *E.g.*, Appx364(100:5-10); Appx1173(283:2-25); Appx1174(286:22-288:2); Appx1248(579:1-11). Amgen’s witnesses confirmed that the patents disclose at least 24 claimed antibodies and showed that generating more was routine in view of the patent’s disclosure. Appx1333-1335(915:13-921:25); Appx1340(940:17-941:25). Dr. Rees explained that with the patent disclosure in hand, it would have been routine to make additional claimed antibodies because “all of these techniques were developed through the 1980s and nineties and were routine in the 2000 decade, in my view." Appx1335(920:11-13); *see also* Appx60; Appx1334(917:14-17); Appx1334-1335(918:18-921:8).

Defendants argue that the "antigen" can only be the entire PCSK9 protein, as opposed to the targeted region of 15 amino acid residues comprising the sweet spot identified in the claims. Br.43-44. But nothing in this Court's decisions would so limit the test. *See, e.g., Centocor*, 636 F.3d at 1352 (this test "applies to disclosure of newly characterized antigens"). The PTO, which derived the test in the first place, has applied it to "antigens" that, like the sweet spot, are targeted regions of proteins. Appx6498(*Bicknell*, at 5); *Ex Parte Supuran*, 2011 WL 1661465, at *2-3 (BPAI Apr. 28, 2011); *Ex Parte Xia*, 2009 WL 220277, at *2, 5 (BPAI Jan. 28, 2009). The purposes of the rule, discussed in Section I.B.2, *supra*, fully support that application.

In any event, whether the recited sweet spot on PCSK9 is an "antigen" was a question of fact argued to the jury. Defendants argued that the "antigen" was the entire PCSK9 protein and thus was known and previously characterized. Br.43-44. Amgen argued that the "antigen" was the small region of 15 amino acids on PCSK9 identified in the claims. The patents define "antigen" as a "molecule or a portion of a molecule" to which an antibody binds. Appx332(36:39-42). In addition, Amgen's experts explained that scientists in the field understand that the term "antigen" is context specific, that it can mean the entire protein or a targeted region of a protein, and that a skilled person reading the patent would understand the "antigen" in Amgen's patent to be the "sweet spot." Appx1313-1314(835:8-836:4); Appx1335(922:5-15); *see also* Appx332(36:39-42). The jury was entitled to credit Amgen's expert testimony on this factual issue.

C. Extensive Evidence Supports The Enablement Verdict.

Although enablement is ultimately a question of law, it relies on underlying factual determinations, including the only contested question here—whether practicing the claimed invention would require undue experimentation. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). That classic jury question requires weighing eight factors. *Id.* at 737. "Enablement is not precluded by the necessity for some experimentation such as routine screening" of antibodies. *Id.* at 736-37; *accord Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998).

The evidence supporting the verdict is overwhelming. Experts on both sides explained that in January 2008 the antibody arts were "mature and well established" and that "it was well-known that you could create antibodies using many different techniques, using the methods that are exemplified and disclosed in the Amgen patents." Appx1340(940:16-941:12); *see also* Appx60; Appx1269-1271(663:16-668:9); Appx1333-1335(915:13-921:3). Biotechnology companies routinely make "many thousands of antibodies" each week using similar methods. Appx1340(941:8-12).

Far from a mere "research plan," Br.58, the patents disclose Amgen's successful execution of that plan, culminating in a "comprehensive roadmap" that teaches the skilled person how make the full scope of claimed antibodies, including non-human antibodies (*e.g.*, mouse or camel antibodies) and antibody fragments. Appx1340(941:15-943:25); *see also* Appx1333-1335(915:13-921:25); Appx1341(944:8-945:2); Appx329(29:61-30:27); Appx331(32:40-42). Defendants' expert agreed, noting that the patent describes "a whole bunch of different ways of making antibodies" and that "everything you can find in the textbook was basically put in there." Appx1278(698:12-14; 699:11-14); *see also* Appx1277(695:10-13).

The jury heard extensive testimony that the level of experimentation needed to practice the invention with the patent's "roadmap" in hand is routine in the art and not "undue." Appx1334-1335(919:25-921:3), Appx1340(941:6-12; 943:14-25). The jury was entitled to credit those facts, and Section 112 requires no more.

III. The District Court Did Not Abuse Its Discretion In Granting A Permanent Injunction.

The court granted an injunction after hearing two days of evidence, weighing each injunction factor, and ultimately concluding that the factors balance in favor of an injunction. Based on the evidence and the court's findings, Defendants cannot show this was an abuse of discretion. *See Robert Bosch, LLC. v. Pylon Mfg.*, 659 F.3d 1142, 1148, 1157 (Fed. Cir. 2011).

Defendants label the injunction "nearly unprecedented" and "shocking," Br.60, but it would have been truly "unprecedented" to deny an injunction and instead impose a compulsory license for the first time in a pharmaceutical case. Drug development is extraordinarily risky, time consuming, and expensive. Appx2332(56:11-23); Appx2379(241:5-

242:6). Injunctions have been routinely granted in pharmaceutical cases in order to protect the investment needed to research new life-saving treatments. *See e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1384 (Fed. Cir. 2006); *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 581 F. Supp. 2d 160, 226-27 (D. Mass. 2008), *aff'd in part*, *rev'd in part on other grounds*, 580 F.3d 1340 (Fed. Cir. 2009); *Janssen Prods., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650 (D.N.J. 2014); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc.*, USA, 821 F. Supp. 2d 681 (D.N.J. 2011).

Surprisingly, Defendants contend that "[r]oyalties are the norm in infringement cases like this one," Br.63, even though they routinely seek injunctions themselves (as in the cases cited above). The grant of a compulsory license in this case would threaten the industry by opening the door to that outcome in all drug cases.

Defendants argue that courts have refused permanent injunctions to promote "public health and choice of products." Br.61. But they cite only a non-precedential decision affirming the denial of a preliminary injunction against a medical device, *Cordis v. Boston Sci.*, 99 F. App'x 928 (Fed. Cir. 2004), and a case holding that a permanent injunction was warranted against smartphones, *Apple v. Samsung Elecs.*, 809 F.3d 633, 647 (Fed. Cir. 2015). Br.61. Their assertion that innovators "often decline even to seek an injunction" is wishful thinking. Br.63.

A. Ongoing Infringement Is Causing Irreparable Harm To Amgen Not Adequately Compensable By Damages.

The court found that Amgen would suffer irreparable harm absent an injunction and that there is no adequate remedy at law. Because "[c]ompetitors change the marketplace," *Polymer Techs. v. Bridwell*, 103 F.3d 970, 975 (Fed. Cir. 1996), they generally cause irreparable harms that are not compensable by damages, including lost market share, price erosion, and lost goodwill. *See Douglas Dynamics, LLC v. Buyers Prods.*, 717 F.3d 1336, 1344 (Fed. Cir. 2013); *see also Merial Ltd. v. Cipla Ltd.*, 681 F.3d 1283, 1306 (Fed. Cir. 2012).

The court found that was the case here, in part because of Amgen's "traditional evidence of loss of market share and momentum." Appx32. Repatha and Praluent "are the only therapeutics in the PCSK9 inhibitor market, making the parties head-to-head competitors in a targeted and developing market." Appx31. The overwhelming evidence was that Praluent and Repatha are completely substitutable. Appx2341-2342(92:3-93:17); Appx2405(347:5-23); Appx4198-4199;

compare Appx2260-2293 *with* Appx2297-2312. This allowed insurers to pit the parties against each other to extract concessions such as unprecedented rebates. Appx2354-2355(143:13-18, 144:20-145:8); Appx2374-2375(224:22-226:12) *see also* Appx2355(145:20-146:3); Appx2356(149:9-17); Appx2359-2360(164:25-165:8). Both experts agree that Praluent's presence on the market has caused price erosion. Appx2375(227:18-228:6); Appx2441(492:4-10).

Moreover, there was evidence that the presence of a competitor has allowed payers to impose strict usage criteria to limit the number of patients receiving Repatha. Appx2355(146:22-148:3); Appx2361(169:12-170:2, 171:23-172:24). There is no way to know what Amgen's revenue would have been without infringement, making any estimate of damages "entirely speculati[ve]." Appx2376(231:20-232:10); Appx2377(234:16-235:12); *see i4i Ltd. P'ship*, 598 F.3d at 862.

The court further relied on the harm to Amgen's reputation as an innovator, harm that it found cannot be quantified in damages. Appx31-32; *see also* Appx2334(61:20-62:4); Appx2356(150:22-151:12); Appx2376(229:20-230:16). Where, as here, the patent holder has a practice of not licensing its patents, Appx2335(67:21-68:20);

Appx2377(235:13-236:9), the right to exclude is an "intangible asset that is part of the company's reputation," *Douglas Dynamics*, 717 F.3d at 1345. Defendants have done their best to injure that reputation by, among other marketing tactics, touting their infringing product as being the first FDA-approved antibody therapy for LDL-C. Appx32; *see* Appx2376(230:19-24); Appx6453.[5]

Amgen's witnesses explained that Amgen invested over two billion dollars over nearly a decade to research, discover, and develop Repatha and that Repatha is critical not only to Amgen's emerging cardiovascular business, but to its business as a whole. Appx2333(60:12-19); Appx2344(62:5-14; 63:4-15); Appx2358-2359(160:20-161:7). Amgen made these investments based on the expectation that Repatha would be protected by its patents, Appx2333(57:15-60:11), and consistent with its business model of using revenue from the sale of existing medicines to recoup the billions of

[5] That no preliminary injunction proceeding took place, a procedural outcome encouraged by the court and Defendants, p. 22 *supra,* does not negate these prospective harms. *Mytee Prods. Inc. v. Harris Research Inc.*, 439 F. App'x 882, 888 (Fed. Cir. 2011) (non-precedential); *see also* 4 Ann. Patent Digest § 32:159:32 (collecting cases).

dollars invested to bring those medicines to market and to fund the costly search for the next life-saving medicines. Appx2332-2333(56:11-57:24).

B. The Balance Of Harms Does Not Favor Infringers Who Knowingly Assume The Risk Of An Injunction.

The court found the balance of harms was "neutral" because both parties made significant investments and would suffer losses to their businesses depending on the ruling. Appx33. Defendants' self-inflicted harms do not swing this factor in their favor.

"One who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected." *Bosch*, 659 F.3d at 1156; *see also i4i*, 598 F.3d at 863. Defendants read Amgen's patent application in 2009, realized there would be a "patent issue," but continued their program at risk. Appx2366-2367(191:4-193:24); Appx2378(237:8-12); Appx2412-2413(376:19-378:15); Appx5698; Appx5683-5691. Even after Amgen filed this suit, Defendants ramped up their spending and leapfrogged Amgen at the FDA. Appx2362(173:16-174:10); Appx2390(285:7-287:8; Appx4524. Then, with a jury trial only eight months away, Defendants launched

Praluent at risk. Appx2378(237:8-12). There is no reason to relieve Defendants of the consequence of their risky business decisions.

C. The Public Interest Is Not Disserved By An Injunction.

1. Defendants and *amici* distort the court's findings.

Defendants assail the injunction decision by claiming the court "expressly found that [an injunction] would *disserve* the public interest" by "revoking a lifesaving drug from patients with no equivalent substitute." Br.4,23 (emphasis in original). But no matter how many times Defendants say it, the court did *not* find that an injunction would "disserve" the public interest. *See* Appx33-34.

Significantly, the court rejected Defendants' argument that an injunction would harm patients because of Praluent's "low dose" option. Appx33. After noting that the FDA approved Repatha to safely and effectively treat all patients covered by the Praluent label, Appx31, Appx33, and reciting Defendants' "low dose" argument, the court refused to "substitute its judgment for that of the FDA" or to "delve into weighing testimony on the propriety of treating patients with the [low] dose of Praluent." Appx33.

The court then considered two interests: the public's interest in enforcing exclusive patent rights and a generalized interest in "having a choice of drugs." Appx33-34. Finding this to be a close call, putting the court "between a rock and a hard place," the court decided that this factor "weighs in favor of defendants" because "having a choice of drugs" is in the public interest. *Id.*

Defendants' challenge to the court's discretionary balancing of the factors is meritless. The court concluded that "plaintiffs have demonstrated irreparable harm, as well as the inadequacy of money damages." Appx34. Balancing those findings with the "public interest factor weigh[ing] in favor of defendants," the court granted the injunction. Appx34.

The grant of injunctive relief in these circumstances follows from this Court's holding that "having more manufacturers of a life-saving good in the market" is not a sufficient basis for denying injunctive relief. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1343 (Fed. Cir. 2016). If that "alone [were] sufficient, it would create a categorical rule denying permanent injunctions for life-saving goods, such as many patented pharmaceutical products." *Id.* At a minimum, concluding that one close factor did not outweigh the others in this case was not a "clear error of judgment," and thus not an abuse of discretion. *Cf. Bosch*, 659 F.3d at 1147.

Defendants argue that the decision deserves no deference because the court did not explain its rationale for the injunction. Br.61-62. But the court evaluated the four injunction factors, examined the evidence for each, and found two in favor of the injunction, one neutral, and one slightly in Defendants' favor. Appx28-34. Because the court performed the proper analysis and made sufficient findings to support its conclusion, Defendants cannot show an abuse of discretion.

2. The injunction does not leave patients without safe, effective treatment.

Defendants and *amici* seek to re-litigate a factual question by arguing that Praluent's "low dose" option allows physicians to treat to a particular LDL-C target level, and that the higher Repatha dose could cause LDL-C to go "too low," thereby putting patients at risk. Br.8,64. But *Amici*'s effort to expand the record adds nothing and is improper as the injunction must be reviewed against the factual record actually before the district court.[6] And Defendants' "low-dose" position is a don't-take-Praluent-off-the-market ploy that Defendants admit is unsupported by any clinical evidence.

The court heard evidence that the FDA considered this very question and approved Repatha as being both safe and effective for all patients for whom Praluent is approved. *Compare* Appx2261 *with* Appx2298. The FDA-approved labeling on both Repatha and Praluent states there is "no evidence" of a safety risk from very low LDL-C levels. *See* Appx2345(105:18-106:12); Appx2264-2265; Appx2301.

The court properly declined to second-guess the FDA. Appx33.

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[6] If extra-record evidence were appropriate, *amici* neglect to mention the most relevant such evidence. Since the trial, Defendants' medical expert, Dr. Eckel, co-authored a paper (funded by Sanofi and Regeneron) reporting that Praluent patients achieved LDL-C levels of 25 mg/dL with no increase in side effects. Ray, K. K., et al., *Reductions in Atherogenic Lipids and Major Cardiovascular Events*, CIRCULATION, 134:1931, 1932 (2016). In November 2016, an Amgen sponsored clinical trial showed that 80% of patients taking Repatha achieved "very low" levels of LDL-C and had a reduction in plaque build-up in their arteries—with no attendant safety concerns. *See* DE108-1 at 8. Most recently, the long-term outcomes trial for Repatha reported that 42 percent of participants taking Repatha (approximately 5,800 patients) had LDL-C levels of 25 mg/dL and saw a reduced risk of myocardial infarction, stroke, and coronary revascularization with no safety concerns. Sabatine, Marc S., et al., *Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease*, N ENGL J MED, p.1,3,5, DOI: 10.1056/NEJMoa1615664 (March 17, 2017).

Defendants and their expert conceded "there is no evidence" of a "safety risk with going too low." Appx2583; Appx2427(435:21-23, 436:10-19). Defendants have asserted that the studies have been too short to observe any ill effects of low LDL-C levels. But outside of litigation, Defendants themselves have stated that "the lower the cholesterol level the better, there is no low limit," and that "concerns about 'too low' LDL" are a mere "marketing issue." Appx2414(383:9-14); Appx4968. Indeed, Defendants' own completed clinical trials for Praluent included more than 900 patients who achieved very low LDL-C levels, below 25 mg/dL, without any safety risk. Appx2343-2344(99:11-101:8); Appx2427(436:16-19); Appx5830; Appx5871-5874.

As the FDA observed, 75 mg Praluent generates similar initial drops as 150 mg Praluent (the dose equivalent to Repatha's 140mg); the main difference is the duration of the lowering effect. Appx2341(89:1-90:5); Appx2341-2342(92:3-93:17); Appx2405(345:11-346:14, 347:5-23); Appx4198-4199. The FDA rejected Defendants' request to market 75 mg Praluent and 150 mg Praluent as achieving distinct levels of LDL-lowering because clinical studies did not support such comparisons—the very type of comparison Defendants are now advancing to this Court.

Appx2406(349:4-350:12); *see also, e.g.*, Appx6475-6476, Appx6487.

Other issues raised by *amici* are not properly before this Court because Defendants did not raise them on appeal. They are also wrong. Defendants' witness could point to no evidence that patients allergic to latex could not use Repatha, and "there were no adverse events in the clinical trials for Repatha with respect to latex." Appx2396(310:17-22). Nor will the need to transition some patients from Praluent to Repatha cause any patients to go without care. Appx2447(515:10-22). In contrast to the unsubstantiated "understanding" of some *amici*, Providers Br.21-23, the record evidence in this case is that insurance contracts can be renegotiated "within 24 to 48 hours." Appx2354(142:14-21). And Amgen's evidence that it can supply the entire demand for PCSK9 antibody products was uncontested. Appx2352(134:12-136:3); Appx2335(67:13-20); Appx2361(170:23-171:18).

Defendants' position is at best speculation, which does not outweigh concrete public interests, *see Stormans, Inc. v. Selecky*, 586 F.3d 1109, 1139 (9th Cir. 2009), such as the interest in encouraging innovation by enforcing exclusive patent rights.

3. The court had discretion to balance the factors.

Defendants try to avoid their burden by arguing that, as a matter of law, *eBay* held that injunctions can *never* issue when the public interest weighs against them. But *eBay rejected* categorical rules of the type now argued by Defendants. *eBay*, 547 U.S. at 394. The sentence quoted by Defendants, Br.59, is not reasonably read to do more than confirm that the proponent of an injunction bears the burden of proof and that the traditional four-factor test applies. *See id.* at 391. Far from altering the traditional balancing of four factors, the Court endorsed it. *Id.*

"Flexibility" has always been the "essence" of the test for injunctive relief. *Hecht Co. v. Bowles*, 321 U.S. 321, 329 (1944). "No one factor, taken individually, is necessarily dispositive." *FMC Corp. v. United States*, 3 F.3d 424, 427 (Fed. Cir. 1993); *accord Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1363 (Fed. Cir. 2013). "The public interest is one factor courts must consider in weighing the equities; it is not dispositive." *Abbott Labs. v. Mead Johnson & Co.*, 971 F.2d 6, 12 n.3 (7th Cir. 1992); *see Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1363-64 (Fed. Cir. 2012) (vacating denial of permanent injunction without disturbing finding that public interest tipped against it); *Smith & Nephew, Inc. v. Interlace Med., Inc.*, 955 F. Supp. 2d 69, 80 (D. Mass. 2013) (granting permanent injunction despite finding public interest favored denial); *Bosch*, 659 F.3d at 1156. Defendants cite no case adopting their rigid reading of *eBay*. *Winter v. NRDC*, 555 U.S. 7, 23 (2008), merely held that the public interest in national security clearly outweighed the other factors on the facts of that case.

The court heard the evidence, evaluated it in light of the correct legal standard, and concluded that an injunction was the appropriate remedy. Defendants fail to show any abuse of discretion.

CONCLUSION

Defendants are admitted infringers who placed a bet that Amgen's patents would be found invalid and lost. They have shown no reason to reverse the jury verdict or the injunction. It is time they stop infringing. The judgment should be affirmed and the permanent injunction order given effect immediately.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify that this paper complies with the type-volume limitation of Fed. Cir. R. 8(b)(1) because it contains 13,927 words, inclusive of 113 words in the figures, excluding the parts of the brief exempted by Fed. R. App. P. 32(f). This paper complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the typestyle requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in 14-point, proportionally spaced typeface using Microsoft Word.

March 24, 2017

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CERTIFICATE OF SERVICE

I certify that on March 24, 2017, I caused the foregoing to be filed with the Court electronically using the CM/ECF system, which will send a notification to all counsel of record.

March 24, 2017

/s/ Daryl L. Joseffer

Daryl L. Joseffer